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(54) Self-filling anti-siphon fluid flow system for particle analysis methods and instruments.

(57) A fluid flow system for use with an analytical instrument is provided having a sample reservoir for holding a liquid suspension of particles to be analyzed, a reagent reservoir for holding a reagent, pump means for pumping fluid to and from the reservoirs to a pumping reservoir, valve means for restricting fluid flow from the reagent reservoir to the pumping reservoir, first conduit means interconnecting the reagent and sample reservoirs, second conduit means connecting the sample and pumping reservoir at a point just behind a metered aperture provided in an end of the second conduit means, and in a preferred embodiment, third conduit means connecting the first and second reservoirs and valve means for restricting fluid flow from the reagent reservoir to the pumping reservoir through the third conduit means, the end of each of the conduit means being maintained at the same physical level.

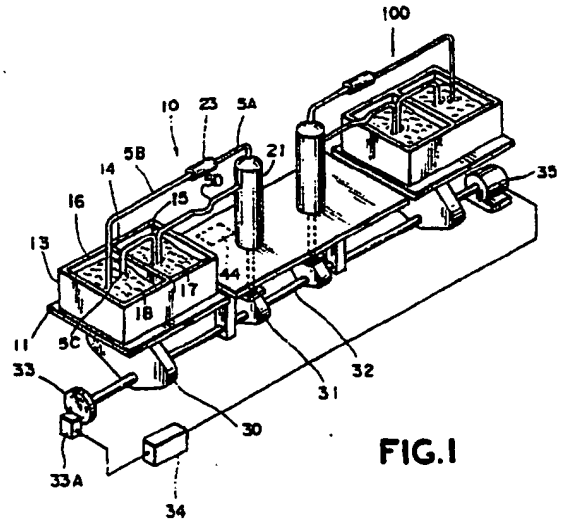

FIG.1

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SELF-FILLING ANTI-SIPHON FLUID FLOW SYSTEM FOR PARTICLE ANALYSIS METHODS AND INSTRUMENTS

The present invention relates to an apparatus and method for effecting liquid flow in an analytical instrument and in particular to those instruments used to analyze biological or industrial samples.

BACKGROUND OF THE INVENTION

Analysis of liquid samples typically involves aspiration of liquid from the sample through a conduit having a metered aperture at its immersed end. The typical particle analyzer consists of three components: a sample vessel, a liquid flow system, and a sensor.

Particle analyzers move suspended biological or industrial particles from the sample vessel to the sensor, via the liquid system. The sensor detects, counts, and identifies the particles. The liquid flow system then moves the sample into a waste container.

Detecting, counting and identifying particles can be done by a variety of sensors. These include impedance, light scatter, and fluorescence type sensors. Regardless of which sensing mechanism is used, the analyzer also needs a liquid flow system.

Many instruments need prepared samples for analysis. The preparation may be as simple as mixing the sample with a reagent. Usually, sample preparation is a two step process. First, the sample is collected in a suitable vessel and then it is prepared by diluting it in salt water. After the analytical cycle is complete, a valve must be closed to prevent draining of the diluent supply from the system by siphon action before new liquid samples are situated for analysis. Conventional liquid flow systems use a combination of pinch valves and/or stopcocks to accomplish this task. These methods are deficient because stopcocks must be manually operated, while normally-closed pinch valves have a tendency to cause a permanent deformation of the system tubing. In addition, most liquid systems for analytical instruments use stepper motors or peristaltic pumps, timing controls, and diluting assemblies. These precision liquid systems are expensive, complex, and require periodic maintenance for reliable operation. This is especially true of systems used to analyze microscopic particles such as red and white blood cells.

In addition, the current design of most particle collection and dilution assemblies have deficiencies in their design and operation which reduce the accuracy- and efficiency of their measurements and the complexity of maintenance. Collectively, these features decrease the efficiency and drastically increase the cost of operation of such analytical instruments. There exists, therefore, a need for a simple yet reliable liquid control system which overcomes these deficiencies by eliminating the pinch valves and manually operated stopcocks yet provides for reliable, low maintenance operation.

It is an object of at least preferred embodiments of the present invention to provide a self-filling, anti-siphon liquid flow system devoid of pinch valves or manually operated stopcocks and which is simple to operate and maintain.

It is an additional object of at least preferred embodiments of this invention to provide an analytical instrument for detecting, counting and identifying particles which has multiple liquid flow subsystems to aspirate samples from multiple sample containers and which may have multiple analytical channels.

SUMMARY OF THE INVENTION

These and other objects are achieved by a fluid flow system for use with an analytical instrument having a sample reservoir for holding a liquid suspension of particles to be analyzed, a reagent reservoir for holding a reagent, pump means for pumping fluid to and from the reservoirs to a pumping reservoir, valve means for restricting fluid flow from the reagent reservoir to the pumping reservoir, first conduit means interconnecting the reagent and sample reservoirs, second conduit means connecting the sample and pumping reservoir at a point just behind a metered aperture provided in an end of the second conduit means, and in a preferred embodiment, third conduit means connecting the first and second reservoirs and valve means for restricting fluid flow from the reagent reservoir to the pumping reservoir through the third conduit means, the end of each of the conduit means being maintained at the same physical level.

BRIEF DESCRIPTION OF THE DRAWINGS

In the following description of the preferred embodiment of the invention, reference is had to the accompanying drawings, in which:

Fig. 1 is a front view of one embodiment of an

analytical instrument in accordance with the present invention;

Fig. 2A-2C are front elevational views of a portion of the system shown in Fig. 1;

Figs. 3A and 3B are front elevational views of the system of Fig. 1 at the time of first use;

Fig. 4A is an enlarged view of the metered aperture area of Figs. 2A-2C, and Fig. 4B is a further enlarged side view of the aperture;

Fig. 5 is a plan view of a modification of the embodiment shown in Fig. 1;

Fig. 6 is a front elevational view of the system shown in Fig. 5; and

Figs. 7A and 7B are enlarged side views of the apertures shown in Figs. 2A-2C and 4A-4B.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Fig. 1 shows an analytical instrument having multiple analyzing sub-stations 10 and 100, each being capable of performing particle analysis on a liquid sample. Figs. 2A-2C are front views of the sub-station 10. Since the sub-stations are essentially the same, their operation will be described with reference only to sub-station 10 as shown in Figs. 2A-2C.

Each sub-station represented by station 10 includes a platform 11 for holding a sample container 13 which is divided into two reservoirs 15 and 16 by dividing wall 14. Reservoir 15 holds a biological or industrial liquid suspension of particles to be analyzed and reservoir 16 holds a reagent 18. Depending on the type of analysis to be perform ed, the liquid sample 17 may be treated by the operator or other personnel before being added to reservoir 15.

A series of conduit members 5A-5D provide intimate liquid contact between reservoirs 15 and 16 and a piston pump 21. Member 5D provides liquid contact between sample reservoir 15 and pump 21. Check valve 23 is disposed between tube members 5A and 5B to permit liquid flow from the pump 21 to reservoir 16 while restricting flow in the opposite direction. Tube member 5C interconnects liquid sample reservoir 15 and reagent reservoir 16 to effect liquid flow therebetween as will be described in greater detail hereinbelow. It is to be understood that the liquid path created by conduit members 5A and 5B is optional. The system operates in accordance with the concepts of the underlying invention without the liquid pathway formed by conduit members 5A and 5B and those skilled in the art will appreciate from the discussion below that they are included for the purpose of increasing the system flow capacity and thus the efficiency of the flow system.

The ends of members 5B, 5C and SD are provided, respectively, with aperture members 5E, 5F and 5G, termed the waste, fill and count apertures in view of their functions within the liquid flow system. In a typical blood cell count analysis, the liquid sample is aspirated through the count aperture 5G which has a sensing mechanism associated with it for detecting and counting each passing cell. The waste aperture 5E and fill aperture 5F are approximately 200 micrometers in diameter, while the diameter of count aperture 5G varies between 45 micrometers for counting red blood cells and 100 micrometers for white cell counting. The diameter of the count aperture corresponds to the diameter of the cell type being counted, thus allowing only one cell to pass through the aperture at a time. Preferably, the waste and fill aperture have a tapered, conical shape as shown in Fig. 7A, while the count aperture is arcuately shaped as shown in Fig. 7B.

During the counting phase of the analytical cycle, liquid is aspirated through fill aperture 5F from the diluent reservoir as a result of the negative pressure produced by downward movement of the piston in pump 21, and supplied through member 5C and around joining wall 2 where it contacts the sample liquid and suspended particles aspirated through aperture 5G at a point 5H just above count aperture 5G, as shown in Figs. 4A and 4B.

As shown in Fig. 4B, the wall 2 adjoining members 5C and 5D terminates at a point 3 which is a greater distance above the aperture opening 5G than a point 6 at which outer wall 7 of member 5C terminates. This structure results in a dynamic operation whereby particles 7, which enter aperture 5G with a velocity V, are entrained by the liquid flowing in member 5C in an area of increased volume. As a result, particles 7 are less likely to collide with and become lodged against wall portion 8.

The bottom surface of aperture member 5G is tapered and elbowed at its rear portion where a passageway 4 is formed. The passageway 4 mates with a conduit member 5J and together they form a chamber through which air is forced. This forced air serves two purposes. First, when the aperture 5G is immersed in the liquid before the count portion of the analytical cycle, the air mixes the solution to create a uniform particle suspension in the reservoir. The mixing process is discontinued during the counting cycle. Second, when the aperture 5G is removed from the reservoir 15, drops that collect on the bottom surface of the aperture will be urged toward the passageway 4 by the inclined surface to a point where the forced air will blow them off the surface.

No liquid is aspirated through waste aperture

5E during the count phase because of the action of check valve 23. When the counting phase is complete, however, liquid flow is reversed by an upward movement of the piston in pump 21 and liquid exits from members 5A and 5B through aperture 5E as well as from members 5C and 5D through apertures 5F and 5G, respectively. When employed in the analytical instrument of the present invention, apertures 5E, 5F and 5G are all kept at the same level.

The operation of a typical working cycle of the analytical instrument will now be described with reference to Figs. 2A-2C.

The mechanical movement of the platform 11 and piston pump 21 is coordinated by a novel cam system including a series of cams 30, 31 mounted on a common cam shaft 32. This system is described in detail in a contemporaneously filed EPO patent application. The rotation of the shaft 32 causes the cams 30 and 31 to move the pump and platform at the proper time in the analytical cycle by virtue of the cam-followers and springs which, in tandem, act to translate the rotational motion of the cams to linear motion for displacement of the platform and pump. An encoder 33 and corresponding sensor 33A detect the relative rotational position of the shaft 32 and relay this information to a controller 34 for interpretation. Based on the relative position information, the controller outputs a stop, start or reverse control signal to motor 35. Wile this cam system is novel, it is not essential to the present invention and those of ordinary skill in the art will appreciate that the description thereof is provided for completeness and also that any method of coordinating and operating the platform and pump could be used in conjunction with the principles disclosed herein.

Before its first use, the liquid flow system shown in Figs. 2A-2C is filled with air. Referring to Fig. 3A, an operator will initially prime the system with a liquid by using a container 13A similar to container 13 but without the dividing wall 14. When initiated; the cam-system lifts the platform to immerse the apertures 5E, 5F and 5G in the liquid in container 13A. The negative pressure created by downward movement of the piston in pump 21 draws liquid into members 5C and 5D through both the fill and count apertures. Despite the vacuum, no liquid is drawn into members 5A and 5B because of the action of check valve 23. As shown in Fig. 3B, at the end of the filling operation, the pump piston is caused to move upward, thereby forcing liquid back to the container 13A through tube members 5C and 5D and through members 5A and 5B through check valve 23. At the end of the upper movement of the piston, tube members 5A, 5B, 5C and 5D are all filled with liquid.

Once primed, the system is ready for liquid sample analysis. After being lowered and removed, the container 13A is replaced by a liquid sample container 13. At this point, the anti-siphon feature of the present invention can be seen. Since the openings are all maintained at the same level, the liquid remaining in the tube members does not drain through apertures 5E, 5F and 5G when the sample containers 13A and 13 are interchanged. The surface tension between the liquid and the side and bottom walls of the tube adjacent the aperture also contribute to this effect.

Referring again to Figs. 2A-2C, once the liquid sample container 13 has been situated, the cam system initiates an analytical cycle of the instrument. Again the piston moves downward within the pump 21 to create a negative relative pressure within the tube members causing liquid from the liquid sample 17 to be drawn up through the count aperture 5G, as indicted by the arrows in Fig. 2A. The count aperture size is chosen as indicated above such that one blood cell can pass through it at a time. A voltage potential U applied between a resistive wire electrode 41 placed in member 5C and plate electrode 42 disposed in sample reservoir 15 causes a current to flow through conducting liquid 17. Appropriate electronics 44 detect the change in current that occurs when a cell passes through the orifice of the aperture member 5G. Each passing cell causes the electronically recorded cell count to increase. The rate at which the piston descends is predetermined in accordance with the size of the aperture to establish a desired liquid flow rate through aperture 5G during the intake phase of the instrument cycle.

At the same time, liquid 18 is drawn into conduit member 5C from the reagent reservoir 16 through fill aperture 5F. Referring to Figs. 4A and 4B, the reagent liquid 18 drawn into member 5C through fill aperture 5F travels along conduit member 5C to a point 5H behind count aperture 5G, where members 5C and 5D are in intimate liquid contact. Some blood cells which enter count aperture 5G will have a tendency to remain at the point 5H just behind the aperture, thus causing interruption of current flow and a false cell count. While the electrical characteristics of these false indications may be recognized and filtered out by appropriate circuitry, in the present system they are eliminated because the flow of reagent liquid 18 at the point of increased volume 5H entrains the lingering cells into the liquid flowing through member 5D, thereby flushing out the area just behind the aperture.

A bubble chamber 20 is formed at the top of the pump cavity for capturing bubbles formed in the liquid flow system. These bubbles are most commonly caused by the build-up of gas particles produced in the electro-chemical reaction at the

count aperture electrodes 41 and 42. These gaseous bubbles travel up through member 5D and are collected in the top of the pump cavity. As shown in Fig. 2B after the count cycle is terminated and the action of the piston in pump 21 is reversed, the liquid and bubbles collected in the piston cavity are caused to exit through the conduit members 5A and 5D, the system being designed so that the volume of liquid collected in the pump is greater than the combined volume of the three tube members. The collected bubbles and liquid are forced through check valve 23 and back into the reagent reservoir 16 through waste aperture 5E, while some of the liquid instead finds its way back into conduit 5C and exits through fill aperture 5F.

Since the liquid collected in the piston cavity during the count cycle exits through apertures 5E, 5F and 5G and is collected only through apertures 5F and 5G, if the flow rate created by pump 2 were the same during the fill and flush phases of the analytical cycle, the pressure across the apertures during each phase would not be the same.

To maintain the pressures across the apertures, it is necessary to increase by twofold the flow rate created by piston pump 21 during the flush portion of the analytical cycle as compared to that created during the fill or count portion. Increasing the flow velocity during the flush portion of the analytical cycle applies a pressure equal in magnitude to, but opposite in polarity to, the pressure during the fill phase. This helps to clear the apertures of any debris. Preferably, the pressure at the count aperture is maintained at six inches of mercury during both phases of liquid flow and the cross-sectional area of the waste aperture 5E is designed to be equal to the sum of the cross-sectional areas of the fill and count apertures 5F and 5G. For red blood cell counting, the fill, count and waste apertures typically have diameters of 200, 45, and 205 micrometers in diameter, respectively. For white cell counting the diameters are typically 200, 100 and 224 micrometers, respectively.

Once the analytical cycle is complete, the platform 11 is lowered as shown in Fig. 2C so that container 13 can be removed and replaced.

Thus, the present system is self-filling, being pumped by a cycle identical to that used for the analytical step. In addition, by maintaining the openings of the various tube members at the same level, the system avoids any possible inaccuracies or contamination that might otherwise be introduced by uncontrolled siphoning of liquid.

Figs. 5 and 6 show another embodiment of the invention wherein additional liquids 51 and 52, contained in reservoirs 53 and 54 must be introduced into the liquid sample reservoir 15. These liquids may be additional liquid samples or other reagents and may be added during or before the actual counting step. Conduit members 51A and 51B provide liquid contact between additional piston pump 55 and reservoir 53 through valve 56, while members 52A and 52B define a liquid path from reservoir 54 to piston pump 57 through valve 58. Conduit members 51C and 52C define, respectively, liquid paths from the pumps 55 and 57 to the liquid sample reservoir 15 through valves 59 and 60.

If liquid 51 must be introduced into reservoir 15, the common shaft cam system would be designed to operate the elements 55, 56 and 59 at the appropriate time in the instrument cycle. First, valve 59 would be closed and valve 56 opened. The piston pump 55 would then aspirate liquid 51 from the reservoir 53 up along member 51A, through valve 56 and into the piston cavity of pump 55 as shown in Fig. 6. After the appropriate amount of liquid 51 was collected in the cavity, valve 56 would be closed and valve 59 opened. The action of piston pump 55 would then be reversed to pump liquid into reservoir 15 through member 51C. This portion of the cycle is shown in Fig. 6 by the combination of valves 58 and 60 with pump 57.

In order to preserve the anti-siphon feature of the system, the open output ends of conduit members 51C and 52C in reservoir 15C should be kept at the same level as the open input ends of members 51A and 52A, respectively, and after completion of the count cycle, valves 56, 58, 59 and 60 should be maintained in the open position.

Referring again to Fig. 1, the operation of the additional analyzing sub-stations is essentially the same as described hereinabove, with the exception of some system timing concerns. In order to reduce the load demand on the motor and thereby decrease the amount of electrical noise introduced into the counting system, the cams are designed so that the piston pump in each sub-station will sequentially effect the counting phase of the cycle before any discharge of liquid, i.e., the pump in station 10 will aspirate liquid through its count aperture to effect a cell count and then the pump in station 100 will draw liquid through its corresponding count aperture before the pump in station 10 begins to output the liquid drawn into its cavity. Once all of the sub-stations have performed their counts, the pumps are forced by the cam system to simultaneously initiate the output phase. Another advantage to this arrangement is that the system only requires one set of counting electronics with a counting signal input switchable between each sub-station of the measurement cycle, since noise created by the operation of the motor is not a concern during the flush portion of the analysis.

Claims

1. A liquid flow system for use with analytical instruments comprising:
a reagent reservoir for holding a quantity of a reagent;
a sample reservoir for holding a quantity of a liquid suspension of particles to be analyzed;
a pumping reservoir;
first conduit means having an upstream end capable of being selectively extended into the reagent reservoir below the normal level of reagent and a downstream end capable of being selectively extended into the sample reservoir below the normal level of liquid in the sample reservoir;
second conduit means having an apertured upstream end capable of being selectively extended into the sample reservoir below the normal level of liquid, the aperture being sized to permit the passage of individual suspended particles from the sample reservoir into the second conduit means, and a downstream end extending into the pumping reservoir;
the upstream and downstream ends of the first conduit means and the apertured upstream end of the second conduit means being at the same level;
the downstream end of the first conduit means being associated with the upstream apertured end of the second conduit means so that reagent liquid from the first conduit means is released into the second conduit means just upstream of the particle-sized aperture and entrains the particles as they enter the second conduit means through the aperture;
first electrode means located in the sample reservoir, second electrode means located in the the second conduit means downstream from the aperture; and
pumping means for drawing reagent through the first conduit means into the second conduit means and for drawing reagent and entrained sample liquid and particles through the second conduit means past the second electrode means and into the pumping reservoir.

2. The system of claim 1 further comprising:
third conduit means having a downstream end capable of being selectively extended into the reagent reservoir for connecting the upper portion of the pumping reservoir and the reagent reservoir and including valve means for permitting flow only from the pumping reservoir to the reagent reservoir, the downstream end of the third conduit means being maintained at the same level as the upstream and downstream ends of the first conduit means and the apertured upstream end of the second conduit means, wherein the pumping means forces reagent and entrained sample liquid and particles collected in the pumping reservoir back through the second conduit means and, having been forced back through the second conduit means, then back through the first conduit means and also forces reagent and entrained sample liquid and particles collected in the pumping means through the third conduit means.

3. The system of claim 2 wherein the pumping reservoir further comprises a bubble chamber formed at a top end thereof for capturing bubbles flowing in the second conduit means when the pump means draws reagent and entrained sample liquid and particles through the second conduit means and for releasing the captured bubbles through the third conduit means and the valve means into the reagent reservoir.

4. The system of claims 1, 2 or 3 wherein a downstream portion of the first conduit means is formed in a unitary manner with an upstream portion of the second conduit means such that reagent drawn into the first conduit means and flowing into the second conduit means entrains the particles drawn into the apertured end of the second conduit means at an area of increased cross-sectional area relative to that of the downstream portion of the second conduit means through which the entraining reagent liquid flows.

5. The system of claim 4 wherein the first conduit means is of a generally inverted U-shape.

6. The system of claim 5 wherein the unitarily formed downstream portion of the first conduit means and the upstream portion of the second conduit means are formed in a single unit which includes a passageway for forced air formed at a rear portion of the unit, the bottom surface of the unit being elbowed at a rear portion and tapered from the rear to a front position where the metered aperture of the second conduit means is disposed such that any drops of liquid collecting on the bottom surface of the unit are urged toward the forced air passageway, and the system further comprises means for forcing air through the forced air passageway.

7. The system of claim 6 wherein the upstream end of the first conduit means and the downstream end of the third conduit means are also provided with apertures chosen such that the cross-sectional area of the aperture of the third conduit means is equal to the sum of the cross-sectional areas of the apertures in each of the first and second conduit means.

8. The system of claim 7 wherein the aperture in the second conduit means is approximately forty-five micrometers in diameter and the aperture in the first conduit means is approximately two hundred micrometers in diameter.

9. The system of claim 7 wherein the aperture in the second conduit means is approximately one hundred micrometers in diameter and the aperture in the first conduit means is approximately two

hundred micrometers in diameter.

10. The system of Claim 7, wherein said pump means is a piston pump having the third reservoir formed therein.

11. The system in accordance with Claim 10, wherein the valve means is a check valve.

12. The system in accordance with Claim 11, wherein the conduit means is a series of flexible tubes.

13. An analytical instrument for analyzing biological or industrial liquid samples comprising one or more liquid flow systems as claimed in any preceding Claim, each further comprising:

means for applying a potential between the first and second electrodes such that a current flows therebetween;

means for detecting a change in the current when an individual suspended particle passes through the apertured upstream end of the second conduit means;

counting means responsive to the detection means for counting the number of particles passing through the apertured upstream end of the second conduit means, said means for applying a potential, said counting means and said detection means all being capable of being switched to each of the sub-stations;

means for coordinating the pumping means and the selective exposure of the apertures; and

means for coordinating the pumping means and the selective exposure of the apertures; and

means responsive to the coordinating means for mechanically effecting the operation of the pumping means and the selective exposure of the apertures.

14. An analytical instrument as claimed in Claim 13, wherein each liquid flow system further comprises a plurality of additional reservoirs for holding, respectively, a plurality of additional reagents:

a plurality of pumps and corresponding additional conduit means each having an upstream end capable of being selectively extended into its corresponding additional reservoir and a downstream end capable of releasing liquid into the reagent reservoir for selectively pumping the reagents in said additional reservoirs along liquid paths to said reagent reservoir, the upstream and downstream ends of each additional conduit means being at the same level;

second valve means for selectively closing and opening the liquid paths from the additional reservoirs to the reagent reservoir; and the coordination means also coordinates the selective pumping of the additional reagents and the opening and closing of said second valve means.

15. A method of analyzing particles comprising:

supplying a quantity of a reagent from a reagent reservoir and a quantity of a liquid suspension of particles to be analyzed from a sample reservoir respectively to first and second conduit means;

providing the second conduit means with an aperture at its upstream end, said aperture being sized to permit the passage of individual suspended particles from the sample reservoir into the second conduit means;

interconnecting a downstream end of the first conduit means and the apertured upstream end of the second conduit means such that reagent flowing in the first conduit means is released into the second conduit means just upstream of the particle-sized aperture and entrains the particles at on area of increased volume as they enter the second conduit means through the aperture;

placing a first electrode in the sample reservoir and a second electrode in the second conduit means downstream from the aperture;

providing pumping means having a pumping reservoir in liquid contact with a downstream end of the second conduit means for drawing reagent through the first conduit means into the second conduit means and for drawing reagent and entrained sample liquid and particles through the second conduit means past the second electrode and into the pumping reservoir;

maintaining an upstream end and the downstream end of the first conduit means and the apertured upstream end of the second conduit means at the same level;

selectively extending the upstream end of the first conduit means into the reagent reservoir below the normal level of reagent and the downstream end of the first conduit means and the upstream end of the second conduit means into the sample reservoir below the normal level of liquid in the sample reservoir;

activating the pumping means to draw liquid from the reagent and sample reservoirs to the pumping reservoir;

counting the number of particles passing by the aperture by measuring the change in current flowing between the first and second electrodes.

16. The method of claim 15 further comprising the step of reversing liquid flow to force reagent and entrained sample liquid and particles collected in the pumping means through the second conduit means and, having been forced back through the second conduit means, then back through the first conduit means.

17. The method of claims 15 or 16 further comprising the steps of:

providing third conduit means having a downstream end capable of extending into the reagent reservoir and an upstream end in liquid contact with the pumping reservoir and valve means for permitting flow through the third conduit means only from the pumping reservoir to the reagent reservoir;

maintaining the downstream end of the third conduit means at the same level as the upstream and downstream ends of the first conduit means and the apertured upstream end of the second conduit means;

selectively extending the downstream end of the third conduit means into the reagent reservoir in coordination with the extension of the upstream and downstream ends of the first conduit means and the upstream end of the second conduit means; and

forcing reagent and entrained sample liquid and particles collected in the pumping means through the third conduit means when the liquid flow is reversed.

18. The method of claim 17 further comprising the steps of collecting bubbles drawn into the pumping reservoir and purging the collected bubbles into the reagent reservoir through the third conduit means.

19. The system of claim 18 wherein the air forcing means forces air through the air passageway to remove any drops urged toward the air passageway along the bottom surface of the unit when the conduit means are removed from the respective reservoirs.

20. The system of Claim 18 or 19, wherein the air forcing means forces air through the air passageway into the sample reservoir to mix the reservoir contents so as to create a uniform particle suspension in the sample reservoir before the drawing action of the pumping means is effected.

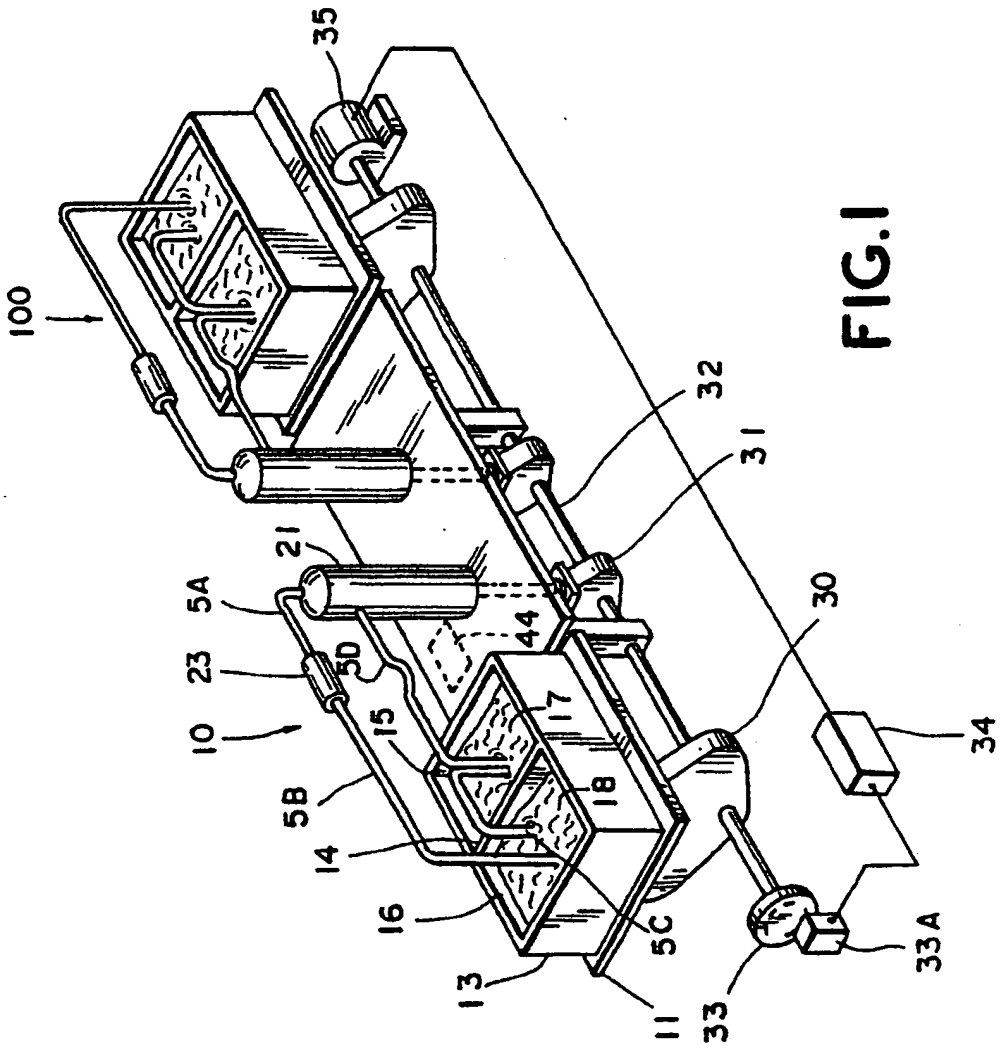

FIG.1

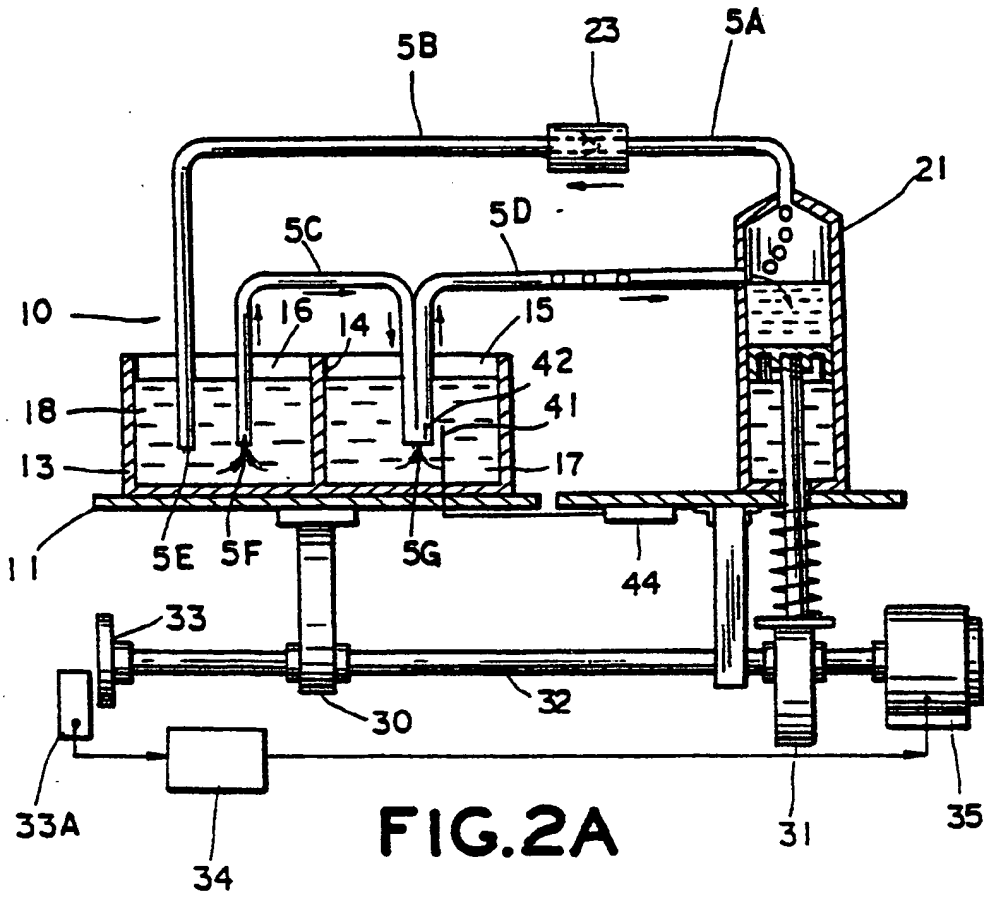
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FIG.2A

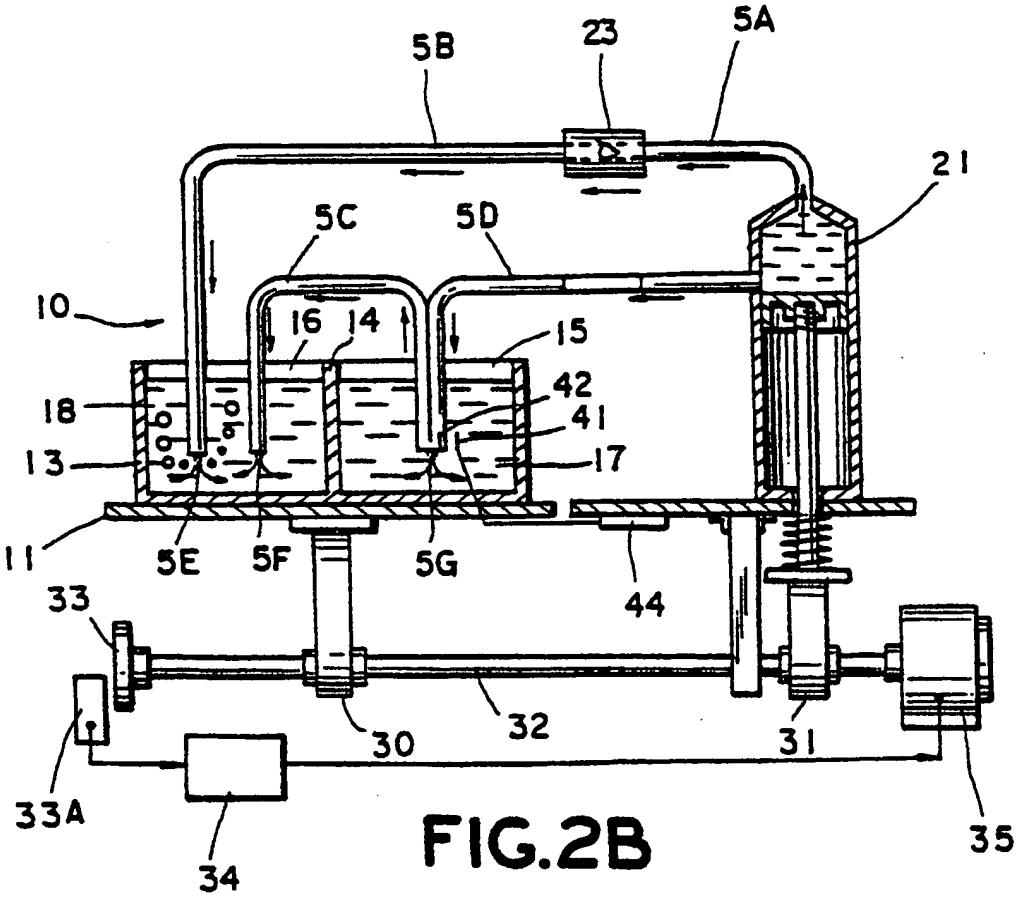
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FIG.2B

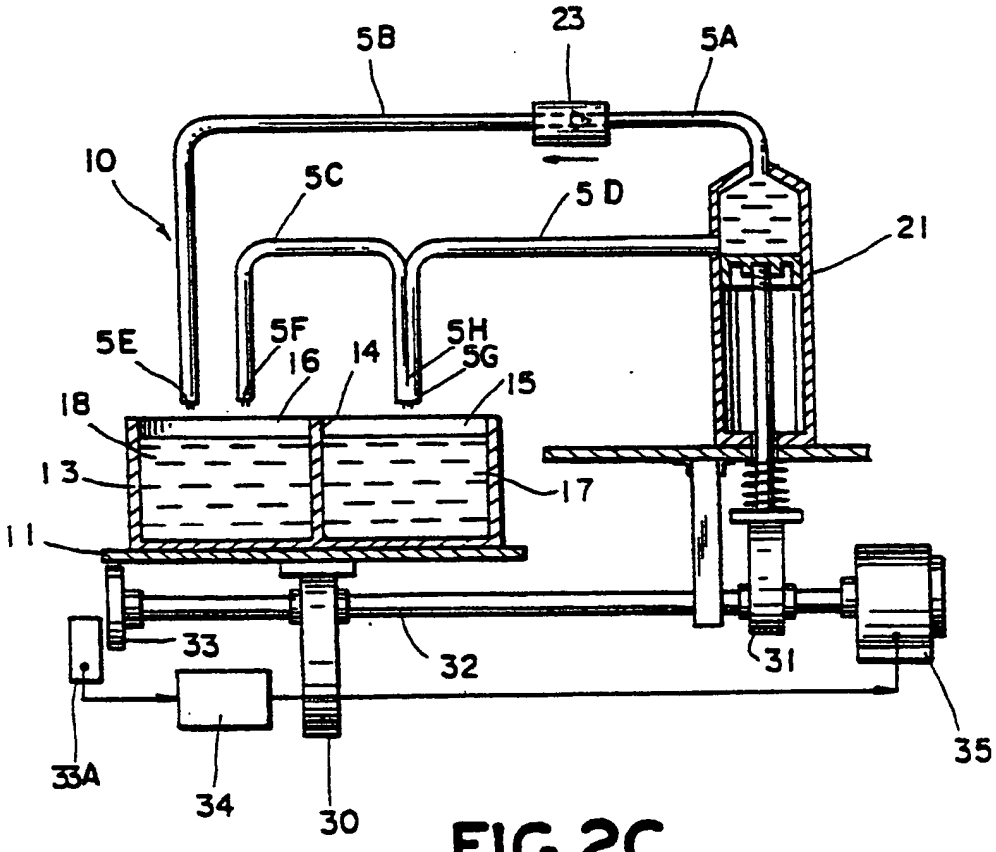
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FIG.2C

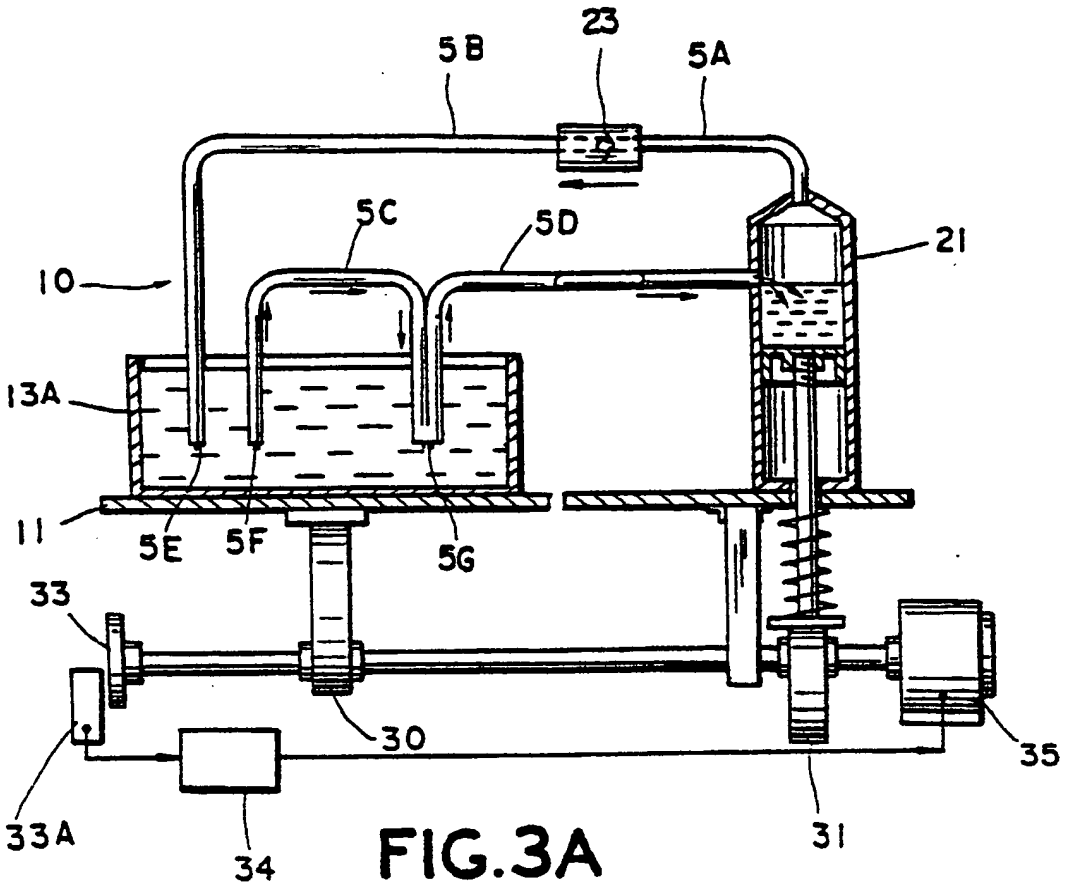

23
5B
5A
5C
5D
21
10
13A
11
5E
5F
5G
33
30
35
33A
34
31

FIG.3A

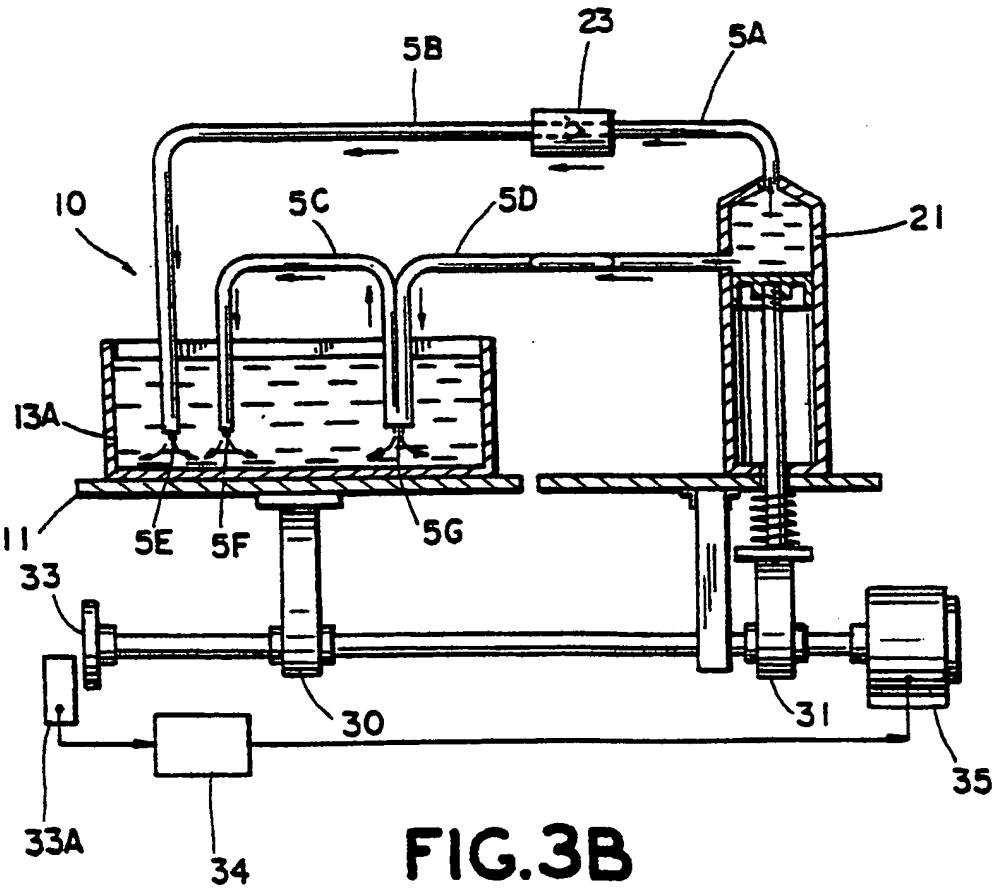

23
5B
5A
10
5C
5D
21
13A
11
5E
5F
5G
33
30
31
35
33A
34

FIG.3B

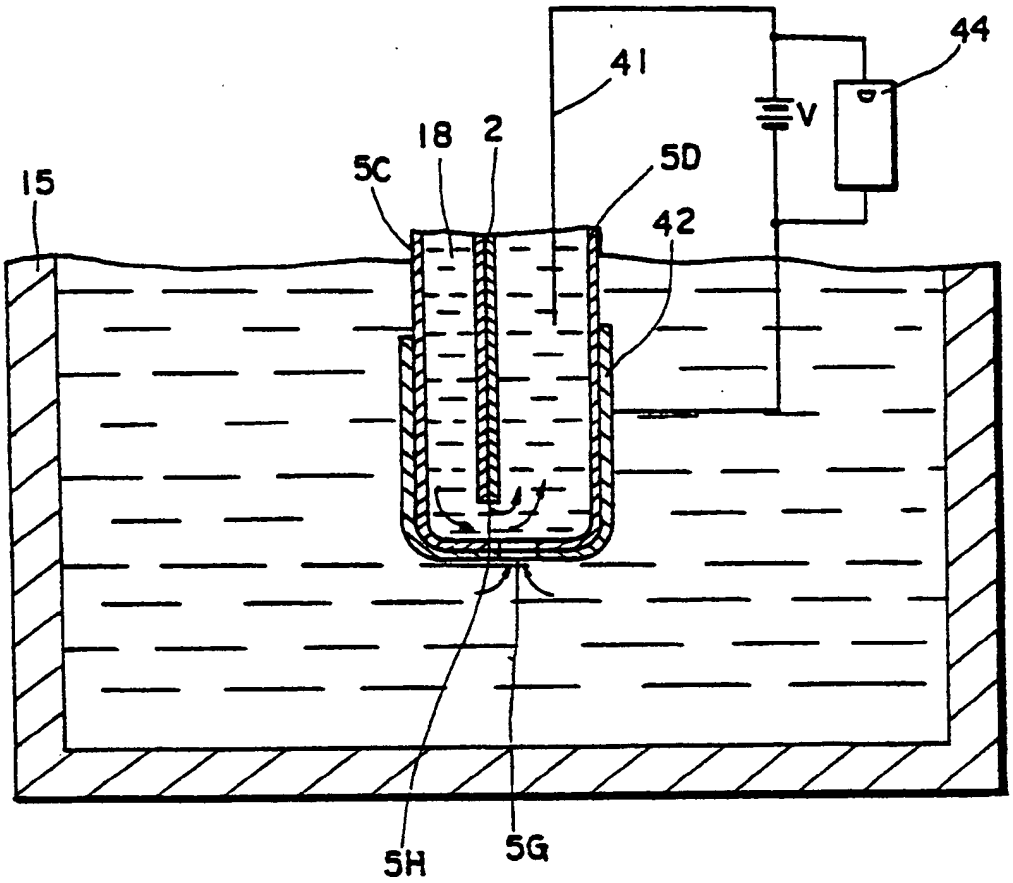


FIG.4A

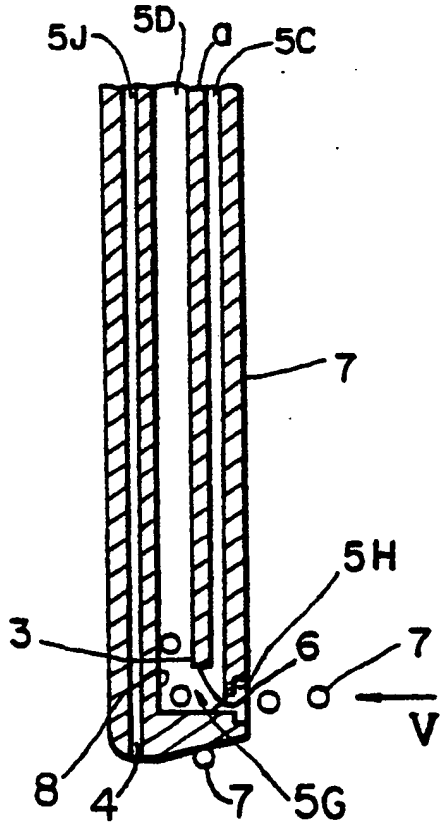
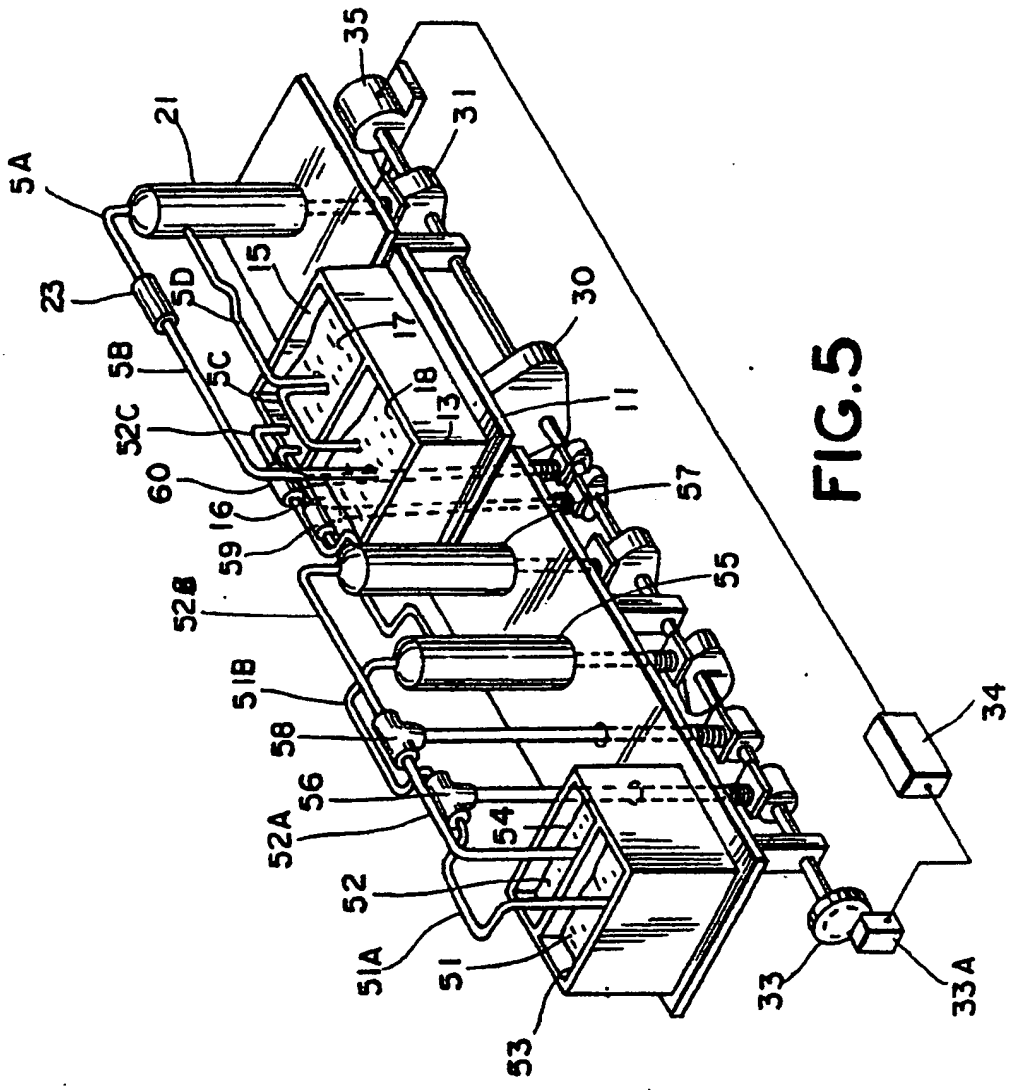


FIG.4B


35
21
31
5A
15
23
5D
30
17
58
5C
18
13
11
52C
60
57
16
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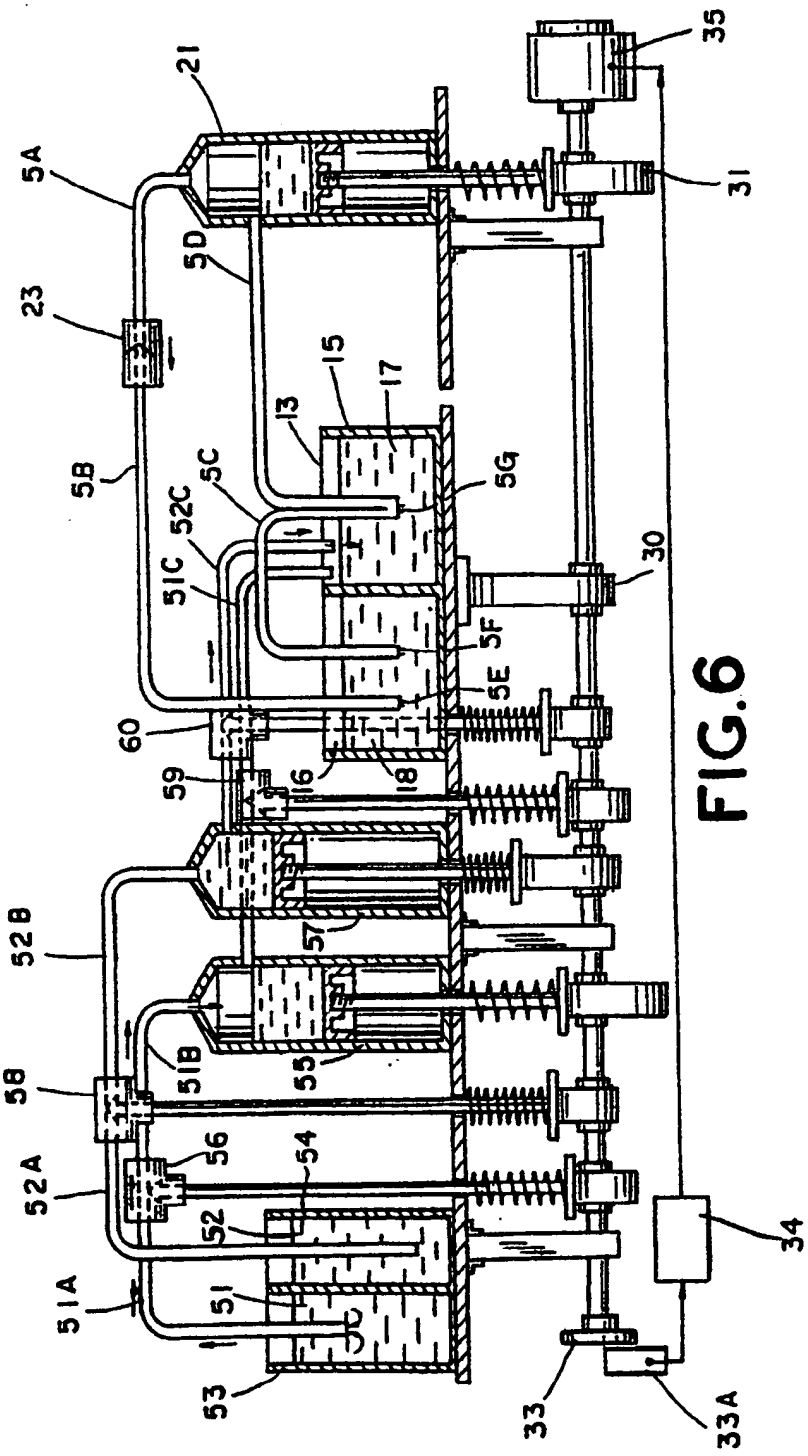
52B
51B
58
34
56
52A
54
52
51A
51
33
33A
53

FIG.5


35
21
5A
31
5D
23
15
17
13
5B
5C
5G
52C
51C
30
5F
5E
60
59
16
18
52B
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51B
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56
54
52A
52
34
51A
51
53
33
33A

FIG.6

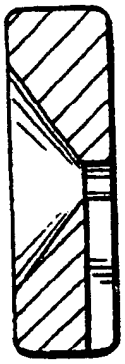

FIG.7A

FIG.7B

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GB-A- 916 238
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US-A- 4 528 158

PATENT ABSTRACTS OF JAPAN vol. 10, no. 364 (P-524)(2421) December 5, 1986 ; & JP-A-61 159 134

PATENT ABSTRACTS OF JAPAN vol. 6, no. 225 (P-154)(1103) November 10, 1982 ; & JP-A-57 127 853

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EP 0 405 729 B1

Description

The present invention relates to an apparatus and method for effecting liquid flow in an analytical instrument and in particular to those instruments used to analyze biological or industrial samples.

BACKGROUND OF THE INVENTION

Analysis of liquid samples typically involves aspiration of liquid from the sample through a conduit having a metered aperture at its immersed end. The typical particle analyzer consists of three components: a sample vessel, a liquid flow system, and a sensor.

Particle analyzers move suspended biological or industrial particles from the sample vessel to the sensor, via the liquid system. The sensor detects, counts, and identifies the particles. The liquid flow system then moves the sample into a waste container.

Detecting, counting and identifying particles can be done by a variety of sensors. These include impedance, light scatter, and fluorescence type sensors. Regardless of which sensing mechanism is used, the analyzer also needs a liquid flow system.

Many instruments need prepared samples for analysis. The preparation may be as simple as mixing the sample with a reagent. Usually, sample preparation is a two step process. First, the sample is collected in a suitable vessel and then it is prepared by diluting it in salt water. After the analytical cycle is complete, a valve must be closed to prevent draining of the diluent supply from the system by siphon action before new liquid samples are situated for analysis. Conventional liquid flow systems use a combination of pinch valves and/or stopcocks to accomplish this task. These methods are deficient because stopcocks must be manually operated, while normally-closed pinch valves have a tendency to cause a permanent deformation of the system tubing. In addition, most liquid systems for analytical instruments use stepper motors or peristaltic pumps, timing controls, and diluting assemblies. These precision liquid systems are expensive, complex, and require periodic maintenance for reliable operation. This is especially true of systems used to analyze microscopic particles such as red and white blood cells.

In addition, the current design of most particle collection and dilution assemblies have deficiencies in their design and operation which reduce the accuracy and efficiency of their measurements and the complexity of maintenance.

Collectively, these features decrease the efficiency and drastically increase the cost of operation of such analytical instruments. There exists, therefore, a need for a simple yet reliable liquid control system which overcomes these deficiencies by eliminating the pinch valves and manually operated stopcocks yet provides for reliable, low maintenance operation.

It is an object of at least preferred embodiments of the present invention to provide a self-filling, anti-siphon liquid flow system devoid of pinch valves or manually operated stopcocks and which is simple to operate and maintain.

It is an additional object of at least preferred embodiments of this invention to provide an analytical instrument for detecting, counting and identifying particles which has multiple liquid flow subsystems to aspirate samples from multiple sample containers and which may have multiple analytical channels.

SUMMARY OF THE INVENTION

A liquid flow system according to the invention is defined in Claim 1 of the accompanying Claims.

A method of analysing particles according to the invention is defined in Claim 15 of the accompanying Claims.

Further features of the invention are defined in the remaining Claims.

A representative prior art liquid flow system is described in US Patent 3 902 115 but has valves in its conduits and lacks provision for selectively extending the ends of the conduits into their respective reservoirs.

BRIEF DESCRIPTION OF THE DRAWINGS

In the following description of the preferred embodiment of the invention, reference is had to the accompanying drawings, in which:

Fig. 1 is a front view of one embodiment of an analytical instrument in accordance with the present invention;

Fig. 2A-2C are front elevational views of a portion of the system shown in Fig. 1;

Figs. 3A and 3B are front elevational views of the system of Fig. 1 at the time of first use;

Fig. 4A is an enlarged view of the metered aperture area of Figs. 2A-2C, and Fig. 4B is a further enlarged side view of the aperture;

Fig. 5 is a plan view of a modification of the embodiment shown in Fig. 1;

Fig. 6 is a front elevational view of the system shown in Fig. 5; and

Figs. 7A and 7B are enlarged side views of the apertures shown in Figs. 2A-2C and 4A-4B.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Fig. 1 shows an analytical instrument having multiple analyzing sub-stations 10 and 100, each being capable of performing particle analysis on a liquid sample. Figs. 2A-2C are front views of the sub-station 10. Since the sub-stations are essentially the same, their operation will be described with reference only to sub-station 10 as shown in Figs. 2A-2C.

Each sub-station represented by station 10 includes a platform 11 for holding a sample container 13 which is divided into two reservoirs 15 and 16 by dividing wall 14. Reservoir 15 holds a biological or industrial liquid suspension of particles to be analyzed and reservoir 16 holds a reagent 18. Depending on the type of analysis to be performed, the liquid sample 17 may be treated by the operator or other personnel before being added to reservoir 15.

A series of conduit members 5A-5D provide intimate liquid contact between reservoirs 15 and 16 and a piston pump 21. Member 5D provides liquid contact between sample reservoir 15 and pump 21. Check valve 23 is disposed between tube members 5A and 5B to permit liquid flow from the pump 21 to reservoir 16 while restricting flow in the opposite direction. Tube member 5C interconnects liquid sample reservoir 15 and reagent reservoir 16 to effect liquid flow therebetween as will be described in greater detail hereinbelow. It is to be understood that the liquid path created by conduit members 5A and 5B is optional. The system operates in accordance with the concepts of the underlying invention without the liquid pathway formed by conduit members 5A and 5B and those skilled in the art will appreciate from the discussion below that they are included for the purpose of increasing the system flow capacity and thus the efficiency of the flow system.

The ends of members 5B, 5C and 5D are provided, respectively, with aperture members 5E, 5F and 5G, termed the waste, fill and count apertures in view of their functions within the liquid flow system. In a typical blood cell count analysis, the liquid sample is aspirated through the count aperture 5G which has a sensing mechanism associated with it for detecting and counting each passing cell. The waste aperture 5E and fill aperture 5F are approximately 200 micrometers in diameter, while the diameter of count aperture 5G varies between 45 micrometers for counting red blood cells and 100 micrometers for white cell counting. The diameter of the count aperture corresponds to the diameter of the cell type being counted, thus allowing only one cell to pass through the aperture at a time. Preferably, the waste and fill aperture have a tapered, conical shape as shown in Fig. 7A, while the count aperture is arcuately shaped as shown in Fig. 7B.

During the counting phase of the analytical cycle, liquid is aspirated through fill aperture 5F from the diluent reservoir as a result of the negative pressure produced by downward movement of the piston in pump 21, and supplied through member 5C and around joining wall 2 where it contacts the sample liquid and suspended particles aspirated through aperture 5G at a point 5H just above count aperture 5G, as shown in Figs. 4A and 4B.

As shown in Fig. 4B, the wall 2 adjoining members 5C and 5D terminates at a point 3 which is a greater distance above the aperture opening 5G than a point 6 at which outer wall 7 of member 5C terminates. This structure results in a dynamic operation whereby particles 7, which enter aperture 5G with a velocity V, are entrained by the liquid flowing in member 5C in an area of increased volume. As a result, particles 7 are less likely to collide with and become lodged against wall portion 8.

The bottom surface of aperture member 5G is tapered and elbowed at its rear portion where a passageway 4 is formed. The passageway 4 mates with a conduit member 5J and together they form a chamber through which air is forced. This forced air serves two purposes. First, when the aperture 5G is immersed in the liquid before the count portion of the analytical cycle, the air mixes the solution to create a uniform particle suspension in the reservoir. The mixing process is discontinued during the counting cycle. Second, when the aperture 5G is removed from the reservoir 15, drops that collect on the bottom surface of the aperture will be urged toward the passageway 4 by the inclined surface to a point where the forced air will blow them off the surface.

No liquid is aspirated through waste aperture 5E during the count phase because of the action of check valve 23. When the counting phase is complete, however, liquid flow is reversed by an upward movement of the piston in pump 21 and liquid exits from members 5A and 5B through aperture 5E as well as from members 5C and 5D through apertures 5F and 5G, respectively. When employed in the analytical instrument of the present invention, apertures 5E, 5F and 5G are all kept at the same level.

The operation of a typical working cycle of the analytical instrument will now be described with reference to Figs. 2A-2C.

The mechanical movement of the platform 11 and piston pump 21 is coordinated by a novel cam system including a series of cams 30, 31 mounted on a common cam shaft 32. This system is described in detail in a contemporaneously filed EPO

patent application (see EP-A-0404321). The rotation of the shaft 32 causes the cams 30 and 31 to move the pump and platform at the proper time in the analytical cycle by virtue of the cam-followers and springs which, in tandem, act to translate the rotational motion of the cams to linear motion for displacement of the platform and pump. An encoder 33 and corresponding sensor 33A detect the relative rotational position of the shaft 32 and relay this information to a controller 34 for interpretation. Based on the relative position information, the controller outputs a stop, start or reverse control signal to motor 35. Wile this cam system is novel, it is not essential to the present invention and those of ordinary skill in the art will appreciate that the description thereof is provided for completeness and also that any method of coordinating and operating the platform and pump could be used in conjunction with the principles disclosed herein.

Before its first use, the liquid flow system shown in Figs. 2A-2C is filled with air. Referring to Fig. 3A, an operator will initially prime the system with a liquid by using a container 13A similar to container 13 but without the dividing wall 14. When initiated, the cam-system lifts the platform to immerse the apertures 5E, 5F and 5G in the liquid in container 13A. The negative pressure created by downward movement of the piston in pump 21 draws liquid into members 5C and 5D through both the fill and count apertures. Despite the vacuum, no liquid is drawn into members 5A and 5B because of the action of check valve 23. As shown in Fig. 3B, at the end of the filling operation, the pump piston is caused to move upward, thereby forcing liquid back to the container 13A through tube members 5C and 5D and through members 5A and 5B through check valve 23. At the end of the upper movement of the piston, tube members 5A, 5B, 5C and 5D are all filled with liquid.

Once primed, the system is ready for liquid sample analysis. After being lowered and removed, the container 13A is replaced by a liquid sample container 13. At this point, the anti-siphon feature of the present invention can be seen. Since the openings are all maintained at the same level, the liquid remaining in the tube members does not drain through apertures 5E, 5F and 5G when the sample containers 13A and 13 are interchanged. The surface tension between the liquid and the side and bottom walls of the tube adjacent the aperture also contribute to this effect.

Referring again to Figs. 2A-2C, once the liquid sample container 13 has been situated, the cam system initiates an analytical cycle of the instrument. Again the piston moves downward within the pump 21 to create a negative relative pressure within the tube members causing liquid from the liquid sample 17 to be drawn up through the count aperture 5G, as indicted by the arrows in Fig. 2A. The count aperture size is chosen as indicated above such that one blood cell can pass through it at a time. A voltage potential U applied between a resistive wire electrode 41 placed in member 5C and plate electrode 42 disposed in sample reservoir 15 causes a current to flow through conducting liquid 17. Appropriate electronics 44 detect the change in current that occurs when a cell passes through the orifice of the aperture member 5G. Each passing cell causes the electronically recorded cell count to increase. The rate at which the piston descends is predetermined in accordance with the size of the aperture to establish a desired liquid flow rate through aperture 5G during the intake phase of the instrument cycle.

At the same time, liquid 18 is drawn into conduit member 5C from the reagent reservoir 16 through fill aperture 5F. Referring to Figs. 4A and 4B, the reagent liquid 18 drawn into member 5C through fill aperture 5F travels along conduit member 5C to a point 5H behind count aperture 5G, where members 5C and 5D are in intimate liquid contact. Some blood cells which enter count aperture 5G will have a tendency to remain at the point 5H just behind the aperture, thus causing interruption of current flow and a false cell count. While the electrical characteristics of these false indications may be recognized and filtered out by appropriate circuitry, in the present system they are eliminated because the flow of reagent liquid 18 at the point of increased volume 5H entrains the lingering cells into the liquid flowing through member 5D, thereby flushing out the area just behind the aperture.

A bubble chamber is formed at the top of the pump cavity for capturing bubbles formed in the liquid flow system. These bubbles are most commonly caused by the build-up of gas particles produced in the electro-chemical reaction at the count aperture electrodes 41 and 42. These gaseous bubbles travel up through member 5D and are collected in the top of the pump cavity. As shown in Fig. 2B after the count cycle is terminated and the action of the piston in pump 21 is reversed, the liquid and bubbles collected in the piston cavity are caused to exit through the conduit members 5A and 5D, the system being designed so that the volume of liquid collected in the pump is greater than the combined volume of the three tube members. The collected bubbles and liquid are forced through check valve 23 and back into the reagent reservoir 16 through waste aperture 5E, while some of the liquid instead finds its way back into conduit 5C and exits through fill aperture 5F.

Since the liquid collected in the piston cavity during the count cycle exits through apertures 5E, 5F and 5G and is collected only through apertures

5F and 5G, if the flow rate created by pump 2 were the same during the fill and flush phases of the analytical cycle, the pressure across the apertures during each phase would not be the same.

To maintain the pressures across the apertures, it is necessary to increase by twofold the flow rate created by piston pump 21 during the flush portion of the analytical cycle as compared to that created during the fill or count portion. Increasing the flow velocity during the flush portion of the analytical cycle applies a pressure equal in magnitude to, but opposite in polarity to, the pressure during the fill phase. This helps to clear the apertures of any debris. Preferably, the pressure at the count aperture is maintained at six inches of mercury during both phases of liquid flow and the cross-sectional area of the waste aperture 5E is designed to be equal to the sum of the cross-sectional areas of the fill and count apertures 5F and 5G. For red blood cell counting, the fill, count and waste apertures typically have diameters of 200, 45, and 205 micrometers in diameter, respectively. For white cell counting the diameters are typically 200, 100 and 224 micrometers, respectively.

Once the analytical cycle is complete, the platform 11 is lowered as shown in Fig. 2C so that container 13 can be removed and replaced.

Thus, the present system is self-filling, being pumped by a cycle identical to that used for the analytical step. In addition, by maintaining the openings of the various tube members at the same level, the system avoids any possible inaccuracies or contamination that might otherwise be introduced by uncontrolled siphoning of liquid.

Figs. 5 and 6 show another embodiment of the invention wherein additional liquids 51 and 52, contained in reservoirs 53 and 54 must be introduced into the liquid sample reservoir 15. These liquids may be additional liquid samples or other reagents and may be added during or before the actual counting step. Conduit members 51A and 51B provide liquid contact between additional piston pump 55 and reservoir 53 through valve 56, while members 52A and 52B define a liquid path from reservoir 54 to piston pump 57 through valve 58. Conduit members 51C and 52C define, respectively, liquid paths from the pumps 55 and 57 to the liquid sample reservoir 15 through valves 59 and 60.

If liquid 51 must be introduced into reservoir 15, the common shaft cam system would be designed to operate the elements 55, 56 and 59 at the appropriate time in the instrument cycle. First, valve 59 would be closed and valve 56 opened. The piston pump 55 would then aspirate liquid 51 from the reservoir 53 up along member 51A, through valve 56 and into the piston cavity of pump 55 as shown in Fig. 6. After the appropriate amount of liquid 51 was collected in the cavity, valve 56 would be closed and valve 59 opened. The action of piston pump 55 would then be reversed to pump liquid into reservoir 15 through member 51C. This portion of the cycle is shown in Fig. 6 by the combination of valves 58 and 60 with pump 57.

In order to preserve the anti-siphon feature of the system, the open output ends of conduit members 51C and 52C in reservoir 15C should be kept at the same level as the open input ends of members 51A and 52A, respectively, and after completion of the count cycle, valves 56, 58, 59 and 60 should be maintained in the open position.

Referring again to Fig. 1, the operation of the additional analyzing sub-stations is essentially the same as described hereinabove, with the exception of some system timing concerns. In order to reduce the load demand on the motor and thereby decrease the amount of electrical noise introduced into the counting system, the cams are designed so that the piston pump in each sub-station will sequentially effect the counting phase of the cycle before any discharge of liquid, i.e., the pump in station 10 will aspirate liquid through its count aperture to effect a cell count and then the pump in station 100 will draw liquid through its corresponding count aperture before the pump in station 10 begins to output the liquid drawn into its cavity. Once all of the sub-stations have performed their counts, the pumps are forced by the cam system to simultaneously initiate the output phase. Another advantage to this arrangement is that the system only requires one set of counting electronics with a counting signal input switchable between each sub-station of the measurement cycle, since noise created by the operation of the motor is not a concern during the flush portion of the analysis.

Claims

1. A liquid flow system for use with analytical instruments comprising:

   a reagent reservoir (16) for holding a quantity of a reagent (18);

   a sample reservoir (15) for holding a quantity of a liquid suspension (17) of particles to be analysed;

   a pumping reservoir;

   first conduit means (5C) between the reagent reservoir (16) and the sample reservoir (15);

   second conduit means (5D) having an upstream end having an aperture (5G) sized to permit the passage of individual suspended particles from the sample reservoir (15) into the second conduit means, and a downstream end extending into the pumping reservoir;

   the downstream end of the first conduit

means (5C) being in fluid communication with the upstream apertured end of the second conduit means (5D) so that reagent liquid (18) from the first conduit means (5C) is released into the second conduit means (5D) through a common passageway located just upstream of the particle sized aperture (5G) and entrains the particles (7) as they enter the second conduit means (5D) through the aperture (5G);

first electrode means (42) located in the sample reservoir (15);

second electrode means (41) located in the second conduit means (5D) downstream from the aperture (5G); and

pumping means (21) for drawing reagent through the first conduit means (5C) into the second conduit means (5D) and for drawing reagent and entrained sample liquid and particles through the second conduit means (5D) past the second electrode means (41) and into the pumping reservoir, characterised in that:

(a) the upstream end (5F) of the first conduit means (5C) is capable of being selectively extended into the reagent reservoir (16) below the normal level of reagent (18) and the downstream end is capable of being selectively extended into the sample reservoir (15) below the normal level of liquid (17) in the sample reservoir;

(b) the second conduit means (5D) has an upstream end capable of being selectively extended into the sample reservoir (15) below the level of liquid (17); and

(c) the upstream and downstream ends and of the first conduit means (5C) and the apertured upstream end of the second conduit (5D) are at the same level.

2. The system of Claim 1 further comprising:

third conduit means (5A,5B) having an downstream end (5E) capable of being selectively extended into the reagent reservoir (16) for connecting the upper portion of the pumping reservoir and the reagent reservoir and including valve means (23) for permitting flow only from the pumping reservoir to the reagent reservoir (16), the downstream end (5E) of the third conduit means being maintained at the same level as the upstream and downstream ends of the first conduit means and the apertured upstream end of the second conduit means (5F,5G), wherein the pumping means (21) forces reagent and entrained sample liquid and particles collected in the pumping reservoir back through the second conduit means (5D) and, having been forced back through the second conduit means (5D) then back through the first conduit means (5C) and also forces reagent and entrained sample liquid and particles collected in the pumping means (21) through the third conduit means (5A,5B).

3. The system according to Claim 2, wherein the valve means (23) is a check valve.

4. The system of Claim 2 or 3, wherein the conduit means (5A-5D) is a series of flexible tubes.

5. The system of Claim 2, 3 or 4, wherein the pumping reservoir further comprises a bubble chamber formed at the top end thereof for capturing bubbles flowing in the second conduit means (5D) when the pump means (21) draws reagent and entrained sample liquid and particles through the second conduit means and for releasing the captured bubbles through the third conduit means (5A,5B) and the valve means (23) into the reagent reservoir (16).

6. The system of any preceding Claim, wherein a downstream portion of the first conduit means (5C) is formed in a unitary manner with an upstream portion of the second conduit means (5D) such that reagent drawn into the first conduit means (5C) and flowing into the second conduit means (5D) entrains the particles drawn into the apertured end (5G) of the second conduit means at an area of increased cross-sectional area relative to that of the downstream portion of the second conduit means (5D) through which the entraining reagent flows.

7. The system of Claim 6, wherein the first conduit means (5C) is of inverted U-shape.

8. The system of Claim 7, wherein the unitarily formed downstream portion of the first conduit means and the upstream portion of the second conduit means are formed into a single unit which includes a passageway (5J) for forced air formed at the rear portion of the unit, the bottom surface of the unit being elbowed at a rear portion and tapered from the rear to a front portion where the metering aperture (5G) of the second conduit means is disposed such that any drops of liquid collecting on the bottom surface of the unit are urged towards the forced air passageway (5J), and the system further comprises means for forcing air through the forced air passageway.

9. The system of Claim 8, wherein the upstream end (5F) of the first conduit means (5C) and the downstream end (5E) of the third conduit

means (5B) are also provided with apertures chosen such that the cross-sectional area of the aperture (5E) of the third conduit means is equal to the sum of the cross sectional areas of the apertures in each of the first and second conduit means (5C,5D).

10. The system of Claim 9, wherein the aperture (5G) in the second conduit means is approximately 45μm in diameter and the aperture (5F) in the first conduit means is approximately 200μm in diameter.

11. The system of Claim 9, wherein the aperture (5G) in the second conduit means is approximately 100μm in diameter and the aperture (5F) in the first conduit means is approximately 200μm in diameter.

12. The system of any preceding Claim, wherein the pumping means (21) is a piston pump having the third reservoir formed therein.

13. An analytical instrument for analysing biological or industrial liquid samples comprising one or more liquid flow systems as claimed in any preceding claim and further comprising:

means for applying a potential between the first and second electrodes such that current flows therebetween;

means for detecting a change in the current when an individual suspended particle passes through the apertured upstream end (5G) of the second conduit means (5D);

counting means responsive to the detection means for counting the number of particles passing through the apertured upstream end of the second conduit means, said means for applying a potential, said counting means and said detection means all being capable of being switched to each of a number of substations;

means for coordinating the pumping means and the selective exposure of the apertures; and

means responsive to the coordinating means for mechanically effecting the operation of the pumping means and the selective exposure of the apertures.

14. An analytical instrument as claimed in Claim 13, wherein each liquid flow system further comprises a plurality of additional reservoirs for holding, respectively, a plurality of additional reagents:

a plurality of pumps and corresponding additional conduit means each having an upstream end capable of being selectively extended into its corresponding additional reservoir and a downstream end capable of releasing liquid into the reagent reservoir for selectively pumping the reagents in said additional reservoirs along the liquid paths to said reagent reservoir, the upstream and downstream ends of each additional conduit means being at the same level;

second valve means for selectively closing and opening the liquid paths form the additional reservoirs to the reagent reservoir; and

wherein the coordination means is also arranged to coordinate the selective pumping of the additional reagents and the opening and closing of the second valve means.

15. A method of analysing particles comprising:

supplying a quantity of a reagent (18) from a reagent reservoir (16) and a quantity of a liquid suspension (17) of particles to be analysed from a sample reservoir (15) respectively to first and second conduit means (5C,5D);

providing the second conduit means with an aperture (5G) at its upstream end, said aperture being sized to permit the passage of individual suspended particles (7) from the sample reservoir (15) into the second conduit means (5G);

interconnecting a downstream end of the first conduit means (5C) and the apertured upstream end (5G) of the second conduit means (5D) such that reagent flowing in the first conduit means is released into the second conduit means just upstream of the particle-sized aperture or area of increased volume as they enter the second conduit means (5D) through the aperture (5G);

placing a first electrode (42) in the sample reservoir and a second electrode (41) in the second conduit means (5D) downstream from the aperture (5G);

providing pumping means (21) having a pumping reservoir in liquid contact with a downstream end of the second conduit means (5D) for drawing reagent through the first conduit means (5C) into the second conduit means (5D) and for drawing reagent and entrained sample liquid particles (7) through the second conduit means (5D) past the second electrode (41) and into the pumping reservoir; characterised by the steps of:

maintaining an upstream end and the downstream end of the first conduit means (5C) and the apertured upstream end of the second conduit means (5D) at the same level;

selectively extending the upstream end of the first conduit means (5C) into the reagent

reservoir (16) below the normal level of reagent (18) and the downstream end of the first conduit means (5C) and the upstream end of the second conduit means (5D) into the sample reservoir (15) below the normal level of liquid (17) in the sample reservoir;

activating the pumping means (21) to draw liquid from the reagent and sample reservoirs (16,15) to the pumping reservoir; and

counting the number of particles passing by the aperture (5G) by measuring the change in current flowing between the first and second electrodes.

16. The method of claim 15, further comprising the steps of reversing liquid flow to force reagent and entrained sample liquid and particles collected in the pumping means (21) through the second conduit means (5D) and, having been forced back through said second conduit means, then back through the first conduit means (5C).

17. The method of Claim 15 or 16, further comprising the steps of:

providing third conduit means (5A,5B) having a downstream end (5E) capable of extending into the reagent reservoir (16) and an upstream end in liquid contact with the pumping reservoir and valve means (23) for permitting flow through the third conduit means only from the pumping reservoir to the reagent reservoir (16);

maintaining the downstream end (5E) of the third conduit means at the same level as the upstream and downstream ends of the first conduit means (5C) and the apertured upstream end of the second conduit means (5D);

selectively extending the downstream end (5E) of the third conduit means (5A,5B) into the reagent reservoir (16) in coordination with the extension of the upstream and downstream ends of the first conduit means (5C) and the upstream end of the second conduit means (5D); and

forcing reagent and entrained sample liquid and particles collected in the pumping means (21) through the third conduit means (5A,5B) when the liquid flow is reversed.

18. The method of Claim 17, further comprising the steps of collecting bubbles drawn into the pumping reservoir and then purging the collected bubbles into the reagent reservoir through the third conduit means (5A,5B).

19. The system of Claim 18, wherein the air forcing means forces air through an air passageway (5J) to remove any drops urged towards the air passageway along the bottom surface of the unit when the conduit means are removed from the respective reservoirs.

Patentansprüche

1. Flüssigkeitsumlaufsystem zum Einsatz mit analytischen Instrumenten mit
einem Reagenzspeicher (16) zum Halten einer Menge eines Reagenz (18);
einem Probenspeicher (15) zum Halten einer Menge einer flüssigen Suspension (17) von zu analysierenden Partikeln;
einem Pumpspeicher;
ersten Leitungseinrichtungen (5C) zwischen dem Reagenzspeicher (16) und dem Probenspeicher (15);
zweiten Leitungseinrichtungen (5D) mit einem aufstromseitigen Ende mit einer Öffnung (5G), die so dimensioniert ist, daß der Durchgang von einzelnen suspendierten Partikeln aus dem Probenspeicher (15) in die zweiten Leitungseinrichtungen ermöglicht wird,
und einem abstromseitigen Ende, das sich in den Pumpspeicher erstreckt;
wobei das abstromseitige Ende der ersten Leitungseinrichtungen (5C) in Strömungsmittelverbindung mit dem aufstromseitigen, mit einer Öffnung versehenen Ende der zweiten Leitungseinrichtungen (5D) steht, so daß Reagenzflüssigkeit (18) von den ersten Leitungseinrichtungen (5C) in die zweiten Leitungseinrichtungen (5D) durch einen gemeinsamen Kanal freigegeben wird, der unmittelbar aufstromseitig der in bezug auf die Partikel dimensionierten Öffnung (5G) angeordnet ist und die Partikel (7) mitführt, wenn sie in die zweiten Leitungseinrichtungen (5D) durch die Öffnung (5G) eindringen;
ersten Elektrodeneinrichtungen (42), die im Probenspeicher (15) angeordnet sind;
zweiten Elektrodeneinrichtungen (41), die in den zweiten Leitungseinrichtungen (5D) abstromseitig der Öffnung (5G) angeordnet sind; und
Pumpeinrichtungen (21) zum Ziehen von Reagenz durch die ersten Leitungseinrichtungen (5C) in die zweiten Leitungseinrichtungen (5D) und zum Ziehen von Reagenz und mitgeführter Probenflüssigkeit und Partikeln durch die zweiten Leitungseinrichtungen (5D) an den zweiten Elektrodeneinrichtungen (41) vorbei und in den Pumpspeicher, dadurch gekennzeichnet, daß
(a) das aufstromseitige Ende (5F) der ersten Leitungseinrichtungen (5C) wahlweise in den Reagenzspeicher (16) unter das norma-

le Niveau des Reagenz (18) verlängert werden kann und das abstromseitige Ende wahlweise in den Probenspeicher (15) unter das normale Niveau der Flüssigkeit (17) im Probenspeicher verlängert werden kann;
(b) die zweiten Leitungseinrichtungen (5D) ein aufstromseitiges Ende besitzen, das wahlweise in den Probenspeicher (15) unter das Niveau der Flüssigkeit (17) verlängert werden kann; und
(c) sich das aufstromseitige und abstromseitige Ende der ersten Leitungseinrichtungen (5C) und das mit der Öffnung versehene aufstromseitige Ende der zweiten Leitungseinrichtungen (5D) auf dem gleichen Niveau befinden.

2. System nach Anspruch 1, das des weiteren umfaßt:
dritte Leitungseinrichtungen (5A, 5B) mit einem abstromseitigen Ende (5E), das wahlweise in den Reagenzspeicher (16) verlängert werden kann, um den oberen Abschnitt des Pumpspeichers und den Reagenzspeicher miteinander zu verbinden, und die Ventileinrichtungen (23) aufweisen, um einen Durchfluß nur vom Pumpspeicher zum Reagenzspeicher (16) zu ermöglichen, wobei das abstromseitige Ende (5E) der dritten Leitungseinrichtungen auf dem gleichen Niveau wie das aufstromseitige und abstromseitige Ende der ersten Leitungseinrichtungen und das mit der Öffnung versehene aufstromseitige Ende der zweiten Leitungseinrichtungen (5F, 5G) gehalten wird und wobei die Pumpeinrichtungen (21) Reagenz und mitgeführte Probenflüssigkeit sowie Partikel, die im Pumpspeicher gesammelt sind, zurück durch die zweiten Leitungseinrichtungen (5D) drücken sowie nach dem Zurückdrücken durch die zweiten Leitungseinrichtungen (5D) dann zurück durch die ersten Leitungseinrichtungen (5C) drücken und ferner Reagenz und mitgeführte Probenflüssigkeit sowie in den Pumpeinrichtungen (21) gesammelte Partikel durch die dritten Leitungseinrichtungen (5A, 5B) drücken.

3. System nach Anspruch 2, bei dem die Ventileinrichtungen (23) ein Rückschlagventil sind.

4. System nach Anspruch 2 oder 3, bei dem die Leitungseinrichtungen (5A-5D) eine Reihe von flexiblen Rohren sind.

5. System nach Anspruch 2, 3 oder 4, bei dem der Pumpspeicher des weiteren eine am oberen Ende desselben ausgebildete Blasenkammer zum Einfangen von Blasen, die in den zweiten Leitungseinrichtungen (5D) strömen, umfaßt, wenn die Pumpeinrichtungen (21) Reagenz und mitgeführte Probenflüssigkeit sowie Partikel durch die zweiten Leitungseinrichtungen ziehen, und zum Freigeben der eingefangenen Blasen durch die dritten Leitungseinrichtungen (5A, 5B) und die Ventileinrichtungen (23) in den Reagenzspeicher (16).

6. System nach einem der vorangehenden Ansprüche, bei dem ein abstromseitiger Abschnitt der ersten Leitungseinrichtungen (5C) einheitlich mit einem aufstromseitigen Abschnitt der zweiten Leitungseinrichtungen (5D) derart ausgebildet ist, daß in die ersten Leitungseinrichtungen (5C) gezogenes und in die zweiten Leitungseinrichtungen (5D) strömendes Reagenz die in das mit der Öffnung versehene Ende (5G) der zweiten Leitungseinrichtungen gezogenen Partikel in einem Bereich von erhöhtem Querschnitt relativ zum abstromseitigen Abschnitt der zweiten Leitungseinrichtungen (5D), durch die das mitgeführte Reagenz strömt, mitführt.

7. System nach Anspruch 6, bei dem die ersten Leitungseinrichtungen (5C) die Form eines umgedrehten U besitzen.

8. System nach Anspruch 7, bei dem der einheitlich geformte abstromseitige Abschnitt der ersten Leitungseinrichtungen und der aufstromseitige Abschnitt der zweiten Leitungseinrichtungen zu einer einzigen Einheit geformt sind, die einen Kanal (5J) für am hinteren Abschnitt der Einheit gebildete Druckluft aufweist, wobei die Bodenfläche der Einheit an einem hinteren Abschnitt ellbogenförmig ausgebildet ist und sich vom hinteren zum vorderen Abschnitt verjüngt, wobei die Dosieröffnung (5G) der zweiten Leitungseinrichtungen derart angeordnet ist, daß jegliche Tropfen der Flüssigkeit, die sich auf der Bodenfläche der Einheit sammeln, zum Druckluftkanal (5J) gedrückt werden, und wobei das System des weiteren Einrichtungen zum Drücken von Luft durch den Druckluftkanal aufweist.

9. System nach Anspruch 8, bei dem das aufstromseitige Ende (5F) der ersten Leitungseinrichtungen (5C) und das abstromseitige Ende (5E) der dritten Leitungseinrichtungen (5B) ebenfalls mit Öffnungen versehen sind, die derart ausgewählt sind, daß der Querschnittsbereich der Öffnung (5E) der dritten Leitungseinrichtungen der Summe der Querschnittsbereiche der Öffnungen in jeder der ersten und zweiten Leitungseinrichtungen (5C, 5D) entspricht.

10. System nach Anspruch 9, bei dem die Öffnung (5G) in den zweiten Leitungseinrichtungen einen Durchmesser von etwa 45 µm und die Öffnung (5F) in den ersten Leitungseinrichtungen einen Durchmesser von etwa 200 µm besitzt.

11. System nach Anspruch 9, bei dem die Öffnung (5G) in den zweiten Leitungseinrichtungen einen Durchmesser von etwa 100 µm und die Öffnung (5F) in den ersten Leitungseinrichtungen einen Durchmesser von etwa 200 µm besitzt.

12. System nach einem der vorangehenden Ansprüche, bei dem die Pumpeinrichtungen (21) eine Kolbenpumpe sind, in der der dritte Speicher ausgebildet ist.

13. Analytisches Instrument zum Analysieren von biologischen oder industriellen Flüssigkeitsproben mit einem oder mehreren Flüssigkeitsumlaufsystemen nach einem der vorangehenden Ansprüche mit
Einrichtungen zum Anlegen eines Potentials zwischen die ersten und zweiten Elektroden, so daß dazwischen ein Strom fließt;
Einrichtungen zum Detektieren einer Stromänderung, wenn ein einzelner suspendierter Partikel das mit der Öffnung versehene aufstromseitige Ende (5G) der zweiten Leitungseinrichtungen (5D) passiert;
Zähleinrichtungen, die auf die Detektionseinrichtungen ansprechen und die Zahl der das mit der Öffnung versehene aufstromseitige Ende der zweiten Leitungseinrichtungen passierenden Partikel zählen, wobei die Einrichtungen zum Anlegen eines Potentials, die Zähleinrichtungen und die Detektionseinrichtungen alle auf jede einer Reihe von Unterstationen geschaltet werden können;
Einrichtungen zum Koordinieren der Pumpeinrichtungen und der wahlweisen Freigabe der Öffnungen; und
Einrichtungen, die auf die Koordinierungseinrichtungen ansprechen, um den Betrieb der Pumpeinrichtungen sowie die wahlweise Freigabe der Öffnungen mechanisch durchzuführen.

14. Analytisches Instrument nach Anspruch 13, bei dem jedes Flüssigkeitsumlaufsystem des weiteren eine Vielzahl von zusätzlichen Speichern zum Halten einer Vielzahl von zusätzlichen Reagenzien umfaßt,
wobei eine Vielzahl von Pumpen und entsprechenden zusätzlichen Leitungseinrichtungen jeweils ein aufstromseitiges Ende besitzen, das wahlweise in den entsprechenden zusätzlichen Speicher verlängert werden kann, sowie ein abstromseitiges Ende, das Flüssigkeit in den Reagenzspeicher abgeben kann, um die Reagenzien in den zusätzlichen Speichern über die Flüssigkeitsbahnen in den Reagenzspeicher zu pumpen, wobei sich die aufstromseitigen und abstromseitigen Enden einer jeden zusätzlichen Leitungseinrichtung auf dem gleichen Niveau befinden;
zweite Ventileinrichtungen zum wahlweisen Schließen und Öffnen der Flüssigkeitsbahnen die zusätzlichen Speicher zum Reagenzspeicher bilden; und
die Koordinierungseinrichtungen auch so angeordnet sind, daß sie das wahlweise Pumpen der zusätzlichen Reagenzien und das Öffnen und Schließen der zweiten Ventileinrichtungen koordinieren.

15. Verfahren zum Analysieren von Partikeln mit den folgenden Schritten
Zuführen einer Menge eines Reagenz (18) aus einem Reagenzspeicher (16) und einer Menge einer flüssigen Suspension (17) von zu analysierenden Partikeln aus einem Probenspeicher (15) zu ersten und zweiten Leitungseinrichtungen (5C, 5D);
Versehen der zweiten Leitungseinrichtungen mit einer Öffnung (5G) an ihrem aufstromseitigen Ende, die so dimensioniert ist, daß sie den Durchgang von einzelnen suspendierten Partikeln (7) vom Probenspeicher (15) in die zweiten Leitungseinrichtungen (5G) ermöglicht;
Verbinden eines abstromseitigen Endes der ersten Leitungseinrichtungen (5C) und des mit der Öffnung versehenen aufstromseitigen Endes (5G) der zweiten Leitungseinrichtungen (5D) derart, daß das in den ersten Leitungseinrichtungen strömende Reagenz in die zweiten Leitungseinrichtungen unmittelbar aufstromseitig der auf die Partikel abgestimmten Öffnung oder eines Bereiches erhöhten Volumens abgegeben wird, wenn die Partikel durch die Öffnung (5G) in die zweiten Leitungseinrichtungen (5D) eindringen;
Anordnen einer ersten Elektrode (42) im Probenspeicher und einer zweiten Elektrode (41) in den zweiten Leitungseinrichtungen (5D) abstromseitig der Öffnung (5G);
Vorsehen von Pumpeinrichtungen (21), die einen Pumpspeicher in Flüssigkeitskontakt mit einem aufstromseitigen Ende der zweiten Leitungseinrichtungen (5D) besitzen, um Reagenz durch die ersten Leitungseinrichtungen (5C) in die zweiten Leitungseinrichtungen (5D) zu ziehen und um Reagenz und mitgeführte Probenflüssigkeitspartikel (7) durch die zweiten Lei-

tungseinrichtungen (5D) an der zweiten Elektrode (41) vorbei in den Pumpspeicher zu ziehen;
gekennzeichnet durch die folgenden Schritte
Aufrechterhalten eines aufstromseitigen Endes und des abstromseitigen Endes der ersten Leitungseinrichtungen (5C) und des mit der Öffnung versehenen aufstromseitigen Endes der zweiten Leitungseinrichtungen (5D) auf dem gleichen Niveau;
wahlweises Verlängern des aufstromseitigen Endes der ersten Leitungseinrichtungen (5C) in den Reagenzspeicher (16) unter das normale Niveau des Reagenz (18) und des abstromseitigen Endes der ersten Leitungseinrichtungen (5C) und des aufstromseitigen Endes der zweiten Leitungseinrichtungen (5D) in den Probenspeicher (15) unter das normale Niveau der Flüssigkeit (17) im Probenspeicher;
Aktivieren der Pumpeinrichtungen (21), um Flüssigkeit aus dem Reagenzspeicher (16) und dem Probenspeicher (15) zum Pumpspeicher abzuziehen; und
Zählen der Anzahl der Partikel, die die Öffnung (5G) passieren, indem die Änderung des zwischen der ersten und zweiten Elektrode fließenden elektrischen Stromes gemessen wird.

16. Verfahren nach Anspruch 15, das des weiteren die Schritte des Umkehrens der Flüssigkeitsströmung umfaßt, um Reagenz und mitgeführte Probenflüssigkeit sowie in den Pumpeinrichtungen (21) gesammelte Partikel durch die zweiten Leitungseinrichtungen (5D) zu drücken und nach dem Zurückführen durch die zweiten Leitungseinrichtungen unter Druck durch die ersten Leitungseinrichtungen (5C) zurückzudrücken.

17. Verfahren nach Anspruch 15 oder 16, das des weiteren folgende Schritte umfaßt:
Vorsehen von dritten Leitungseinrichtungen (5A, 5B) mit einem abstromseitigen Ende (5E), das in den Reagenzspeicher (16) verlängert werden kann, und einem aufstromseitigen Ende in Flüssigkeitskontakt mit dem Pumpspeicher sowie Ventileinrichtungen (23), um einen Durchfluß durch die dritten Leitungseinrichtungen nur vom Pumpspeicher zum Reagenzspeicher (16) zu ermöglichen;
Aufrechterhalten des abstromseitigen Endes (5E) der dritten Leitungseinrichtungen auf dem gleichen Niveau wie das aufstromseitige Ende und die abstromseitigen Enden der ersten Leitungseinrichtungen (5C) und das mit der Öffnung versehene aufstromseitige Ende der zweiten Leitungseinrichtungen (5D);
wahlweises Verlängern des abstromseitigen Endes (5E) der dritten Leitungseinrichtungen (5A, 5B) in den Reagenzspeicher (16) in Koordination mit der Verlängerung des aufstromseitigen Endes und der abstromseitigen Enden der ersten Leitungseinrichtungen (5C) und des aufstromseitigen Endes der zweiten Leitungseinrichtungen (5D); und
Drücken von Reagenz und mitgeführter Probenflüssigkeit sowie den in den Pumpeinrichtungen (21) gesammelten Partikeln durch die dritten Leitungseinrichtungen (5A, 5B), wenn der Flüssigkeitsstrom reversiert wird.

18. Verfahren nach Anspruch 17, das des weiteren die Schritte des Sammelns von in den Pumpspeicher gezogenen Blasen und danach des Abführens der gesammelten Blasen in den Reagenzspeicher durch die dritten Leitungseinrichtungen (5A, 5B) umfaßt.

19. System nach Anspruch 18, bei dem die Luftdruckeinrichtungen Luft durch einen Luftkanal (5J) drücken, um jedwede Tropfen zu entfernen, die in Richtung auf den Luftkanal entlang der Bodenfläche der Einheit gedrückt werden, wenn die Leitungseinrichtungen von den entsprechenden Speichern entfernt werden.

Revendications

1. Système d'écoulement de liquide destiné à être utilisé avec des instruments d'analyse comprenant:
un réservoir de réactif (16) pour contenir une quantité de réactif (18) ;
un réservoir d'échantillon (15) pour contenir une quantité d'une suspension liquide (17) de particules à analyser ;
un réservoir de pompage ;
un premier moyen de conduit (5C) placé entre le réservoir de réactif (16) et le réservoir d'échantillon (15) ;
un second moyen de conduit (5D) comportant une extrémité amont présentant une ouverture (5G) dimensionnée afin de permettre le passage des particules individuelles en suspension venant du réservoir d'échantillon (15) dans le second moyen de conduit et une extrémité aval s'étendant dans le réservoir de pompage;
l'extrémité aval du premier moyen de conduit (5C) étant en communication de fluide avec l'extrémité amont ouverte du second moyen de conduit (5D) de sorte que le liquide réactif (18) issu du premier moyen de conduit (5C) soit libéré dans le second moyen de conduit (5D) à travers un passage commun situé juste en amont de l'ouverture dimension-

née pour les particules (5G) et entraîne les particules (7) lorsqu'elles entrent dans le second moyen de conduit (5D) à travers l'ouverture (5G) ;

un premier moyen d'électrode (42) placé dans le réservoir d'échantillon (15) ;

un second moyen d'électrode (41) placé dans le second moyen de conduit (5D) en aval de l'ouverture (5G) ; et

des moyens de pompage (21) destinés à attirer le réactif à travers le premier moyen de conduit (5C) dans le second moyen de conduit (5D) et à attirer le réactif et le liquide d'échantillon entraîné et les particules à travers le second moyen de conduit (5D) au-delà du second moyen d'électrode (41) et dans le réservoir de pompage ,

caractérisé en ce que :

(a) l'extrémité amont (5F) du premier moyen de conduit (5C) est capable d'être sélectivement étendue dans le réservoir de réactif (16) au-dessous du niveau normal du réactif (18) et en ce que l'extrémité aval est capable d'être sélectivement étendue dans le réservoir d'échantillon (15) au-dessous du niveau normal de liquide (17) dans le réservoir d'échantillon ;

(b) le second moyen de conduit (5D) comporte une extrémité amont capable d'être sélectivement étendue dans le réservoir d'échantillon (15) au-dessous du niveau de liquide (17) ; et

(c) les extrémités amont et aval du premier moyen de conduit (5C) et l'extrémité amont ouverte du second moyen de conduit (5D) se trouvent au même niveau .

2. Système selon la revendication 1 comprenant de plus :

un troisième moyen de conduit (5A, 5B) comportant une extrémité aval (5E) capable d'être sélectivement étendue dans le réservoir de réactif (16) en vue de raccorder la partie supérieure du réservoir de pompage et le réservoir de réactif et incluant un moyen de vanne (23) pour permettre un écoulement seulement à partir du réservoir de pompage vers le réservoir de réactif (16), l'extrémité aval (5E) du troisième moyen de conduit étant maintenue au même niveau que les extrémités aval et amont du premier moyen de conduit et que l'extrémité amont ouverte du second moyen de conduit (5F, 5G) , dans lequel le moyen de pompage (21) force le réactif et le liquide d'échantillon entraîné et les particules collectées dans le réservoir de pompage à repasser à travers le second moyen de conduit (5D) et, ayant été forcé en retour à travers le second moyen de conduit (5D) à revenir ensuite à travers le premier moyen de conduit (5C) et force également le réactif et le liquide échantillon entrainé et les particules collectées dans le moyen de pompage (21) à travers le troisième moyen de conduit (5A, 5B).

3. Système selon la revendication 2 , dans lequel le moyen de vanne (23) est une soupape de non retour.

4. Système selon la revendication 2 ou 3, dans lequel le moyen de conduit (5A-5D) est une série de tubes souples.

5. Système selon la revendication 2,3 ou 4, dans lequel le réservoir de pompage comprend de plus une chambre à bulles formée au niveau de son extrémité supérieure pour piéger les bulles circulant dans le second moyen de conduit (5D) lorsque le moyen de pompage (21) attire le réactif et le liquide échantillon entraîné et les particules à travers le second moyen de conduit et pour libérer les bulles capturées à travers le troisième moyen de conduit (5A, 5B) et le moyen de vanne (23) dans le réservoir de réactif (16).

6. Système selon l'une quelconque des revendications précédentes , dans lequel une partie aval du premier moyen de conduit (5C) est formée de manière solidaire avec une partie amont du second moyen de conduit (5D) de telle sorte que le réactif attiré dans le premier moyen de conduit (5C) et s'écoulant dans le second moyen de conduit (5D) entraîne les particules attirées dans l'extrémité ouverte (5G) du second moyen de conduit au niveau d'une zone de surface transversale accrue par rapport à celle de la partie aval du second moyen de conduit (5D) à travers laquelle le réactif d'entraînement s'écoule.

7. Système selon la revendication 6, dans lequel le premier moyen de conduit (5C) présente une forme de U renversé.

8. Système selon la revendication 7, dans lequel la partie aval formée de façon solidaire du premier moyen de conduit et la partie amont du second moyen de conduit forment une unité unique qui inclut un passage (5J) destiné à l'air forcé formé au niveau de la partie arrière de l'unité , la surface inférieure de l'unité étant coudée au niveau d'une partie arrière et inclinée à partir de l'arrière vers une partie avant où l'ouverture de mesure (5G) du second moyen de conduit est disposée de telle sorte

que toutes les gouttes de liquide recueillies sur la surface inférieure de l'unité soient poussées vers le passage d'air forcé (5J) et le système comprend de plus des moyens pour forcer l'air à travers le passage d'air forcé.

9. Système selon la revendication 8, dans lequel l'extrémité amont (5F) du premier moyen de conduit (5C) et l'extrémité aval (5E) du troisième moyen de conduit (5B) sont également pourvues d'ouvertures choisies de façon que la surface de section transversale de l'ouverture (5E) du troisième moyen de conduit soit égale à la somme des surfaces des sections transversales des ouvertures dans chacun des premier et second moyens de conduit (5C, 5D).

10. Système selon la revendication 9, dans lequel l'ouverture (5G) dans le second moyen de conduit a un diamètre d'approximativement 45 µm et l'ouverture (5F) dans le premier moyen de conduit a un diamètre d'approximativement 200 µm.

11. Système selon la revendication 9, dans lequel l'ouverture (5G) dans le second moyen de conduit a un diamètre d'environ 100 µm et l'ouverture (5F) dans le premier moyen de conduit a un diamètre d'environ 200 µm.

12. Système selon l'une quelconque des revendications précédentes , dans lequel le moyen de pompage (21) est une pompe à piston comportant, formé en elle, le troisième réservoir.

13. Instrument d'analyse pour analyser des échantillons liquides biologiques ou industriels comprenant un ou plusieurs systèmes d'écoulement de liquide tels que revendiqués dans l'une quelconque des revendications précédentes et comprenant de plus :

un moyen pour appliquer un potentiel entre les première et seconde électrodes de façon qu'un courant circule entre elles ;

un moyen pour détecter une variation de courant lorsqu' une particule individuelle en suspension passe à travers l'extrémité amont ouverte (5G) du second moyen de conduit ;

un moyen de comptage sensible au moyen de détection pour compter le nombre de particules passant à travers l'extrémité amont ouverte du second moyen de conduit , ledit moyen pour appliquer un potentiel, ledit moyen de comptage et ledit moyen de détection pouvant tous être commutés à chaque sous-station d'un certain nombre de sous-stations ;

un moyen pour coordonner le moyen de pompage et l'exposition sélective des ouvertures ; et

un moyen sensible au moyen de coordination pour effectuer mécaniquement le fonctionnement du moyen de pompage et l'exposition sélective des ouvertures .

14. Instrument d'analyse selon la revendication 13, dans lequel chaque système d'écoulement de liquide comprend de plus une pluralité de réservoirs supplémentaires pour contenir, respectivement, une pluralité de réactifs additionnels ;

une pluralité de pompes et de moyens de conduit supplémentaires correspondants comportant chacun une extrémité amont capable d'être étendue sélectivement dans son réservoir additionnel correspondant et une extrémité aval capable de libérer le liquide dans le réservoir de réactif pour pomper sélectivement les réactifs dans lesdits réservoirs additionnels le long des trajets de liquide vers ledit réservoir de réactif , les extrémités amont et aval de chaque moyen de conduit supplémentaire étant au même niveau ;

un second moyen de vanne pour fermer et ouvrir sélectivement les parcours de liquide des réservoirs supplémentaires vers le réservoir de réactif ; et

dans lequel le moyen de coordination est également agencé pour coordonner le pompage sélectif des réactifs supplémentaires et l'ouverture et la fermeture du second moyen de vanne.

15. Méthode d'analyse de particules consistant à :

fournir une quantité de réactif (18) provenant d'un réservoir de réactif (16) et une quantité de suspension liquide (17) de particules à analyser provenant d'un réservoir d'échantillon (15) respectivement vers un premier et un second moyen de conduit (5C, 5D) ;

prévoir le second moyen de conduit avec une ouverture (5G) au niveau de son extrémité amont , ladite ouverture étant dimensionnée pour permettre le passage des particules individuelles en suspension (7) du réservoir d'échantillon (15) dans le second moyen de conduit (5G) ;

interconnecter une extrémité aval du premier moyen de conduit (5C) et l'extrémité amont ouverte (5G) du second moyen de conduit (5D) de telle sorte qu'un réactif s'écoulant dans le premier moyen de conduit soit libéré dans le second moyen de conduit juste en amont de l'ouverture dimensionnée pour les particules ou de la zone de volume accru

lorsqu'elles entrent dans le second moyen de conduit (5D) par l'ouverture (5G) ;

placer une première électrode (42) dans le réservoir d'échantillon et une seconde électrode (41) dans le second moyen de conduit (5D) en aval de l'ouverture (5G) ;

fournir un moyen de pompage (21) comportant un réservoir de pompage en contact liquide avec une extrémité aval du second moyen de conduit (5D) pour attirer le réactif à travers le premier moyen de conduit (5C) dans le second moyen de conduit (5D) et pour attirer le réactif et les particules du liquide échantillon entrainées (7) à travers le second moyen de conduit (5D) après la seconde électrode (41) et dans le réservoir de pompage ; caractérisée par les étapes consistant à :

maintenir une extrémité amont et l'extrémité aval du premier moyen de conduit (5C) et l'extrémité amont ouverte du second moyen de conduit (5D) au même niveau;

étendre sélectivement l'extrémité amont du premier moyen de conduit (5C) dans le réservoir de réactif (16) au-dessous du niveau normal du réactif (18) et l'extrémité aval du premier moyen de conduit (5C) et l'extrémité amont du second moyen de conduit (5D) dans le réservoir d'échantillon (15) au-dessous du niveau normal du liquide (17) dans le réservoir d'échantillon ;

activer le moyen de pompage (21) pour attirer le liquide des réservoirs de réactif et d'échantillon (16, 15) vers le réservoir de pompage ; et

compter le nombre de particules passant par l'ouverture (5G) en mesurant la variation de courant circulant entre les première et seconde électrodes .

16. Méthode selon la revendication 15, comprenant de plus l'étape consistant à inverser l'écoulement de liquide pour forcer le réactif et l'échantillon liquide entraîné et les particules recueillies dans le moyen de pompage (21) à travers le second moyen de conduit (5D) et , après avoir été forcés en retour à travers ledit second moyen de conduit , a retourner ensuite à travers le premier moyen de conduit (5C).

17. Méthode selon la revendication 15 ou 16, comprenant de plus les étapes consistant à :

fournir un troisième moyen de conduit (5A, 5B) comportant une extrémité aval (5E) capable de s'étendre dans le réservoir de réactif (16) et une extrémité amont en contact liquide avec le réservoir de pompage et un moyen de vanne (23) pour permettre un écoulement à travers le troisième conduit seulement à partir du réservoir de pompage vers le réservoir de réactif (16);

maintenir l'extrémité aval (5E) du troisième moyen de conduit au même niveau que les extrémités amont et aval du premier moyen de conduit (5C) et que l'extrémité amont ouverte du second moyen de conduit (5D) ;

étendre sélectivement l'extrémité aval (5E) du troisième moyen de conduit (5A, 5B) dans le réservoir de réactif (16) en coordination avec l'extension des extrémités amont et aval du premier moyen de conduit (5C) et l'extrémité amont du second moyen de conduit (5D) ; et

forcer le réactif et l'échantillon liquide entrainé et les particules collectées dans le moyen de pompage (21) à travers le troisième moyen de conduit (5A, 5B) lorsque l'écoulement de liquide est inversé.

18. Méthode selon la revendication 17 , comprenant de plus les étapes consistant à collecter les bulles attirées dans le réservoir de pompage et ensuite à purger les bulles collectées dans le réservoir de réactif à travers le troisième moyen de conduit (5A, 5B) .

19. Système selon la revendication 18, dans lequel le moyen de forçage de l'air force l'air à travers un passage d'air (5J) pour éliminer toutes les gouttes poussées vers le passage d'air le long de la surface inférieure de l'unité lorsque les moyens de conduit sont retirés des réservoirs respectifs .

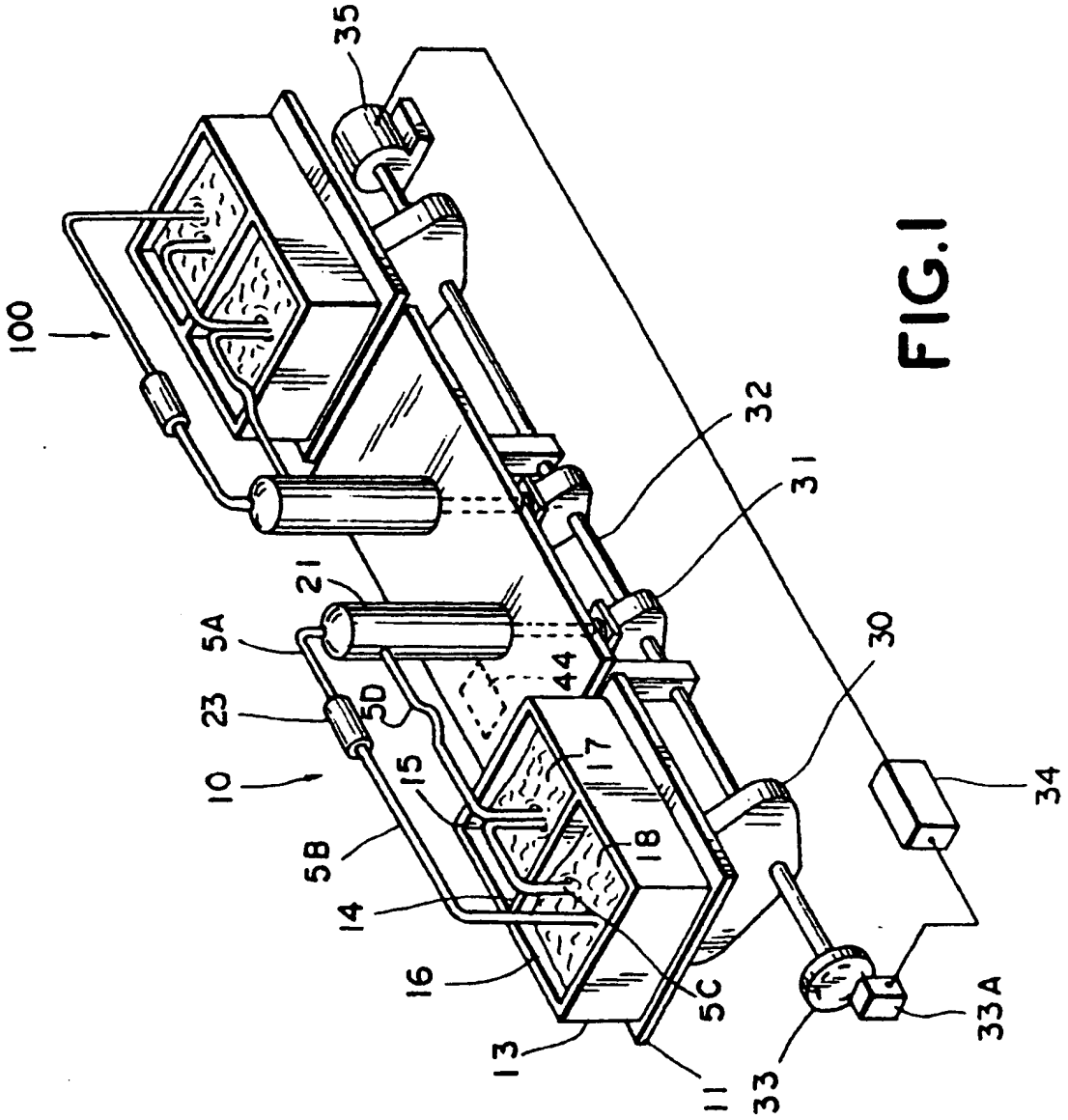

FIG.1

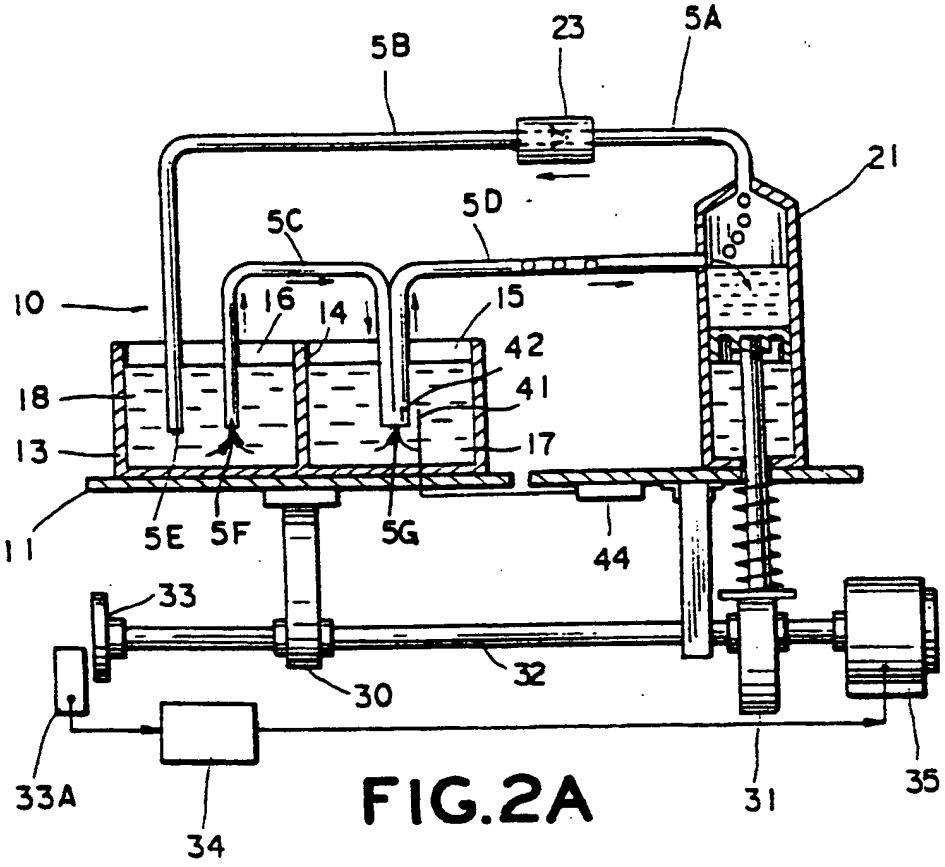
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FIG.2A

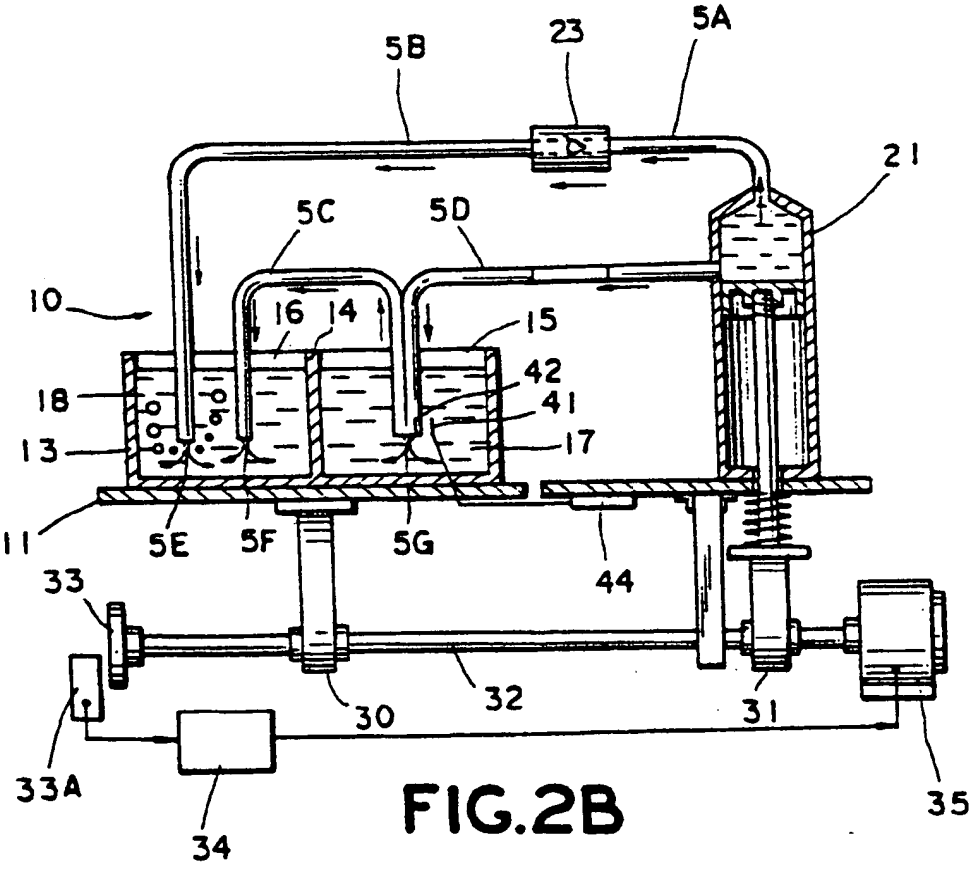
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FIG.2B

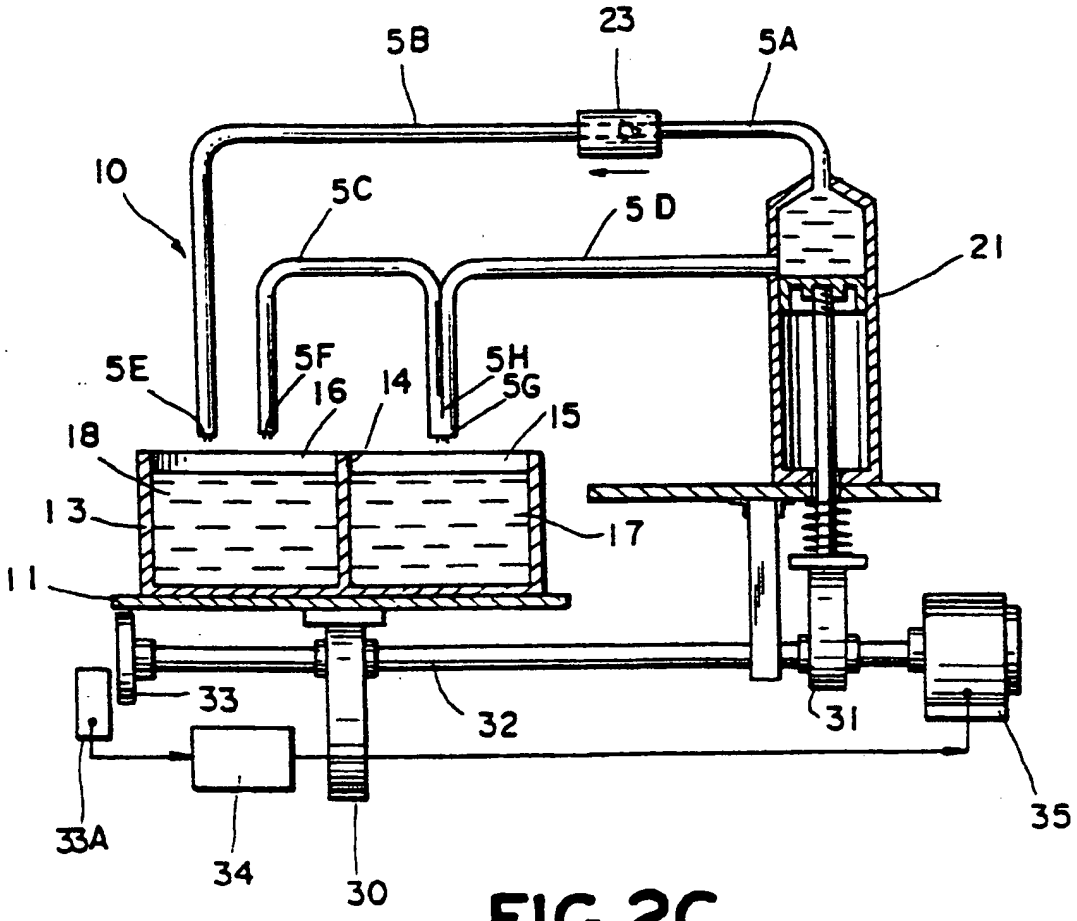
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FIG.2C

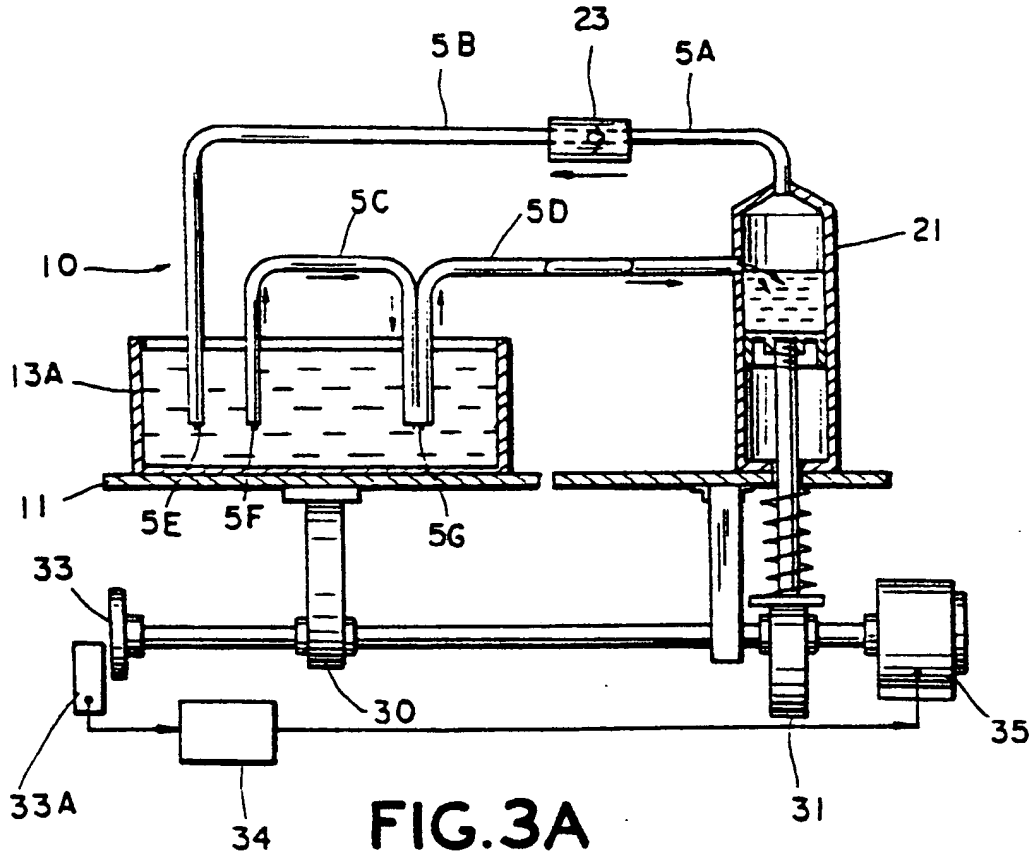
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FIG.3A

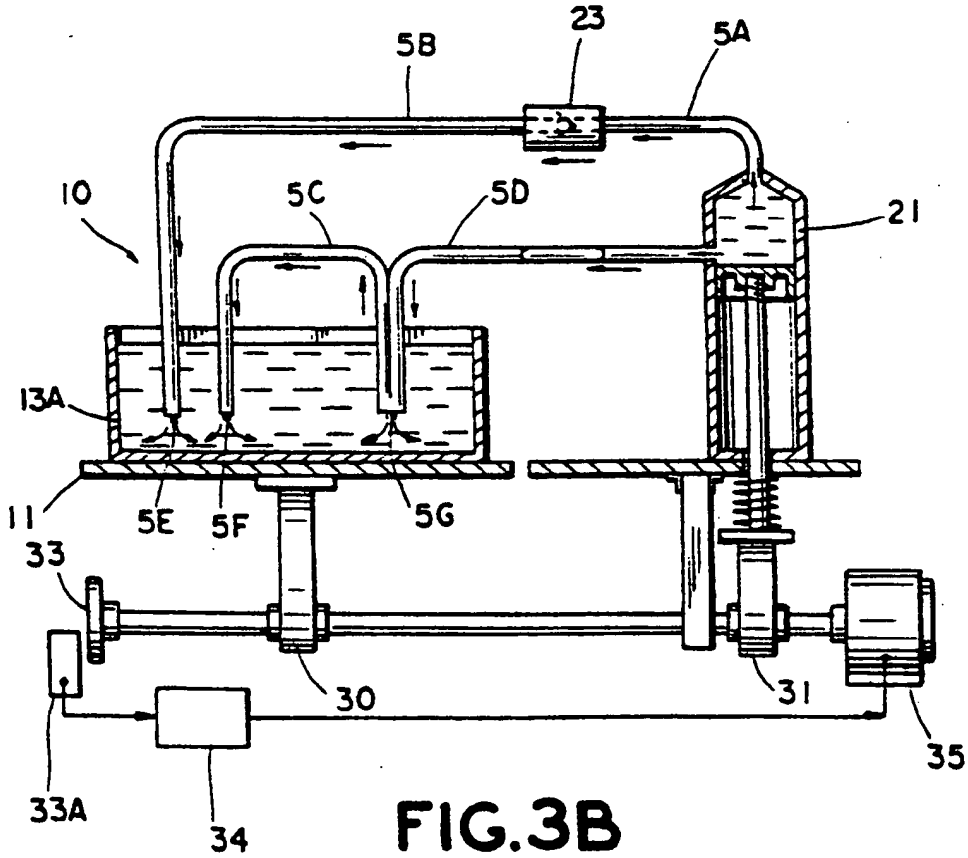
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FIG.3B

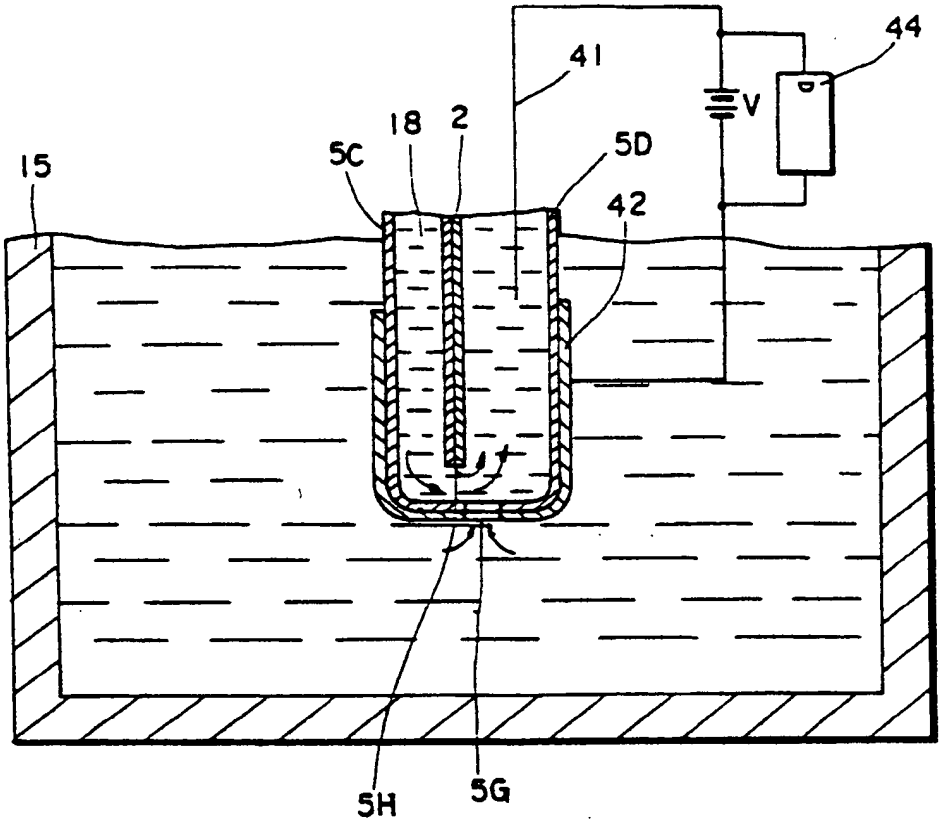

FIG.4A

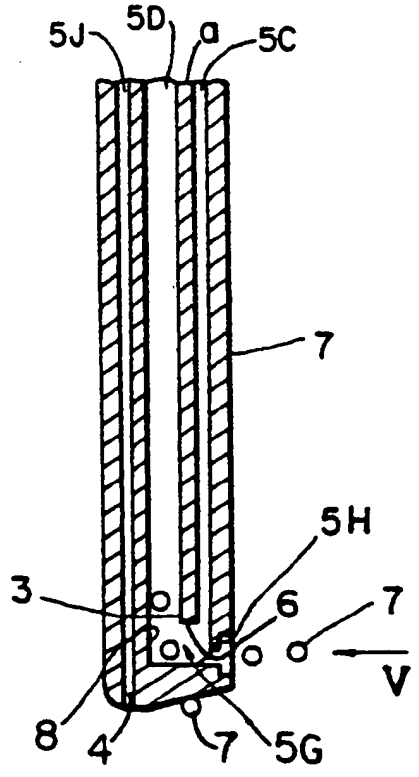

FIG.4B

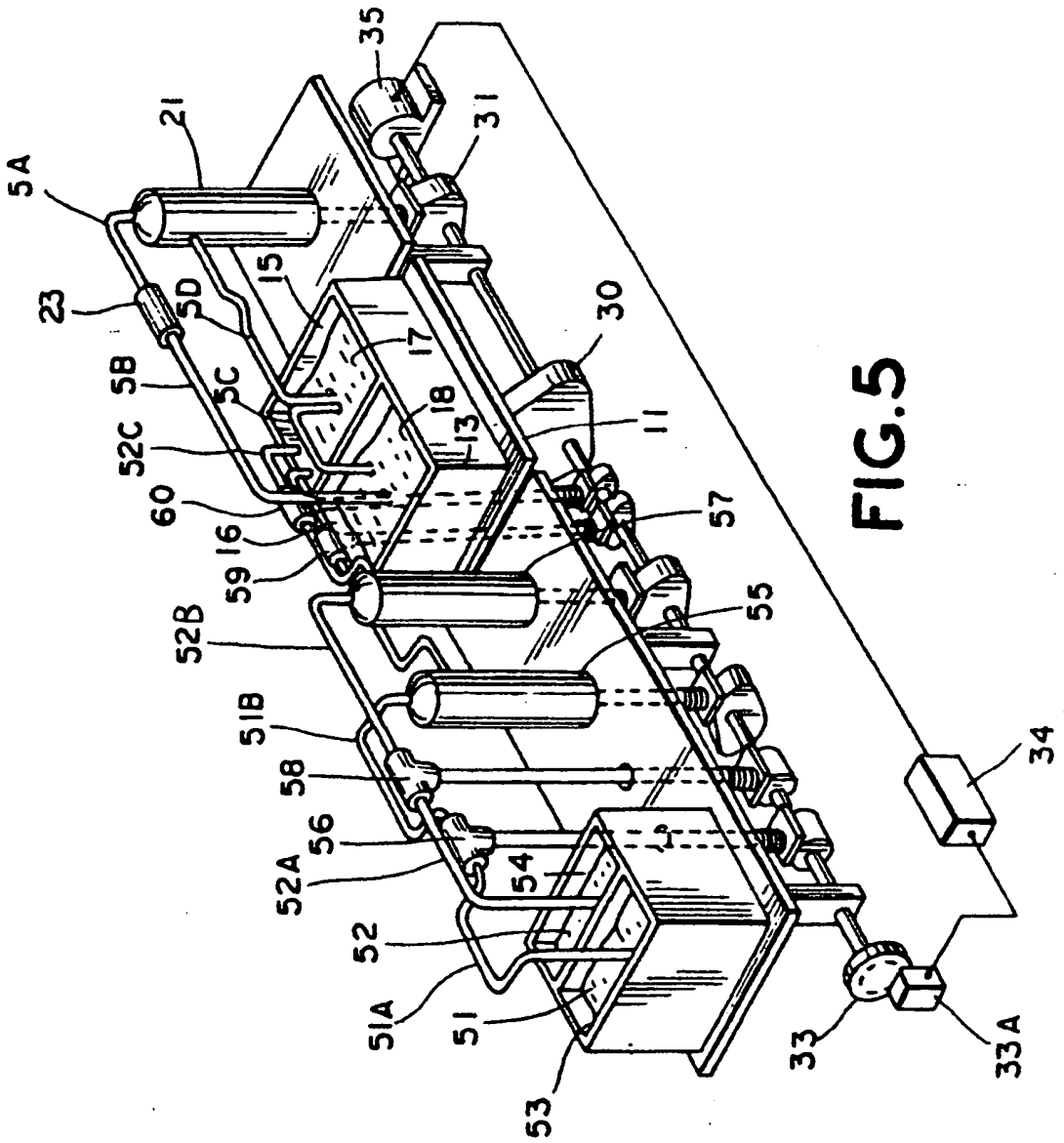
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FIG.5

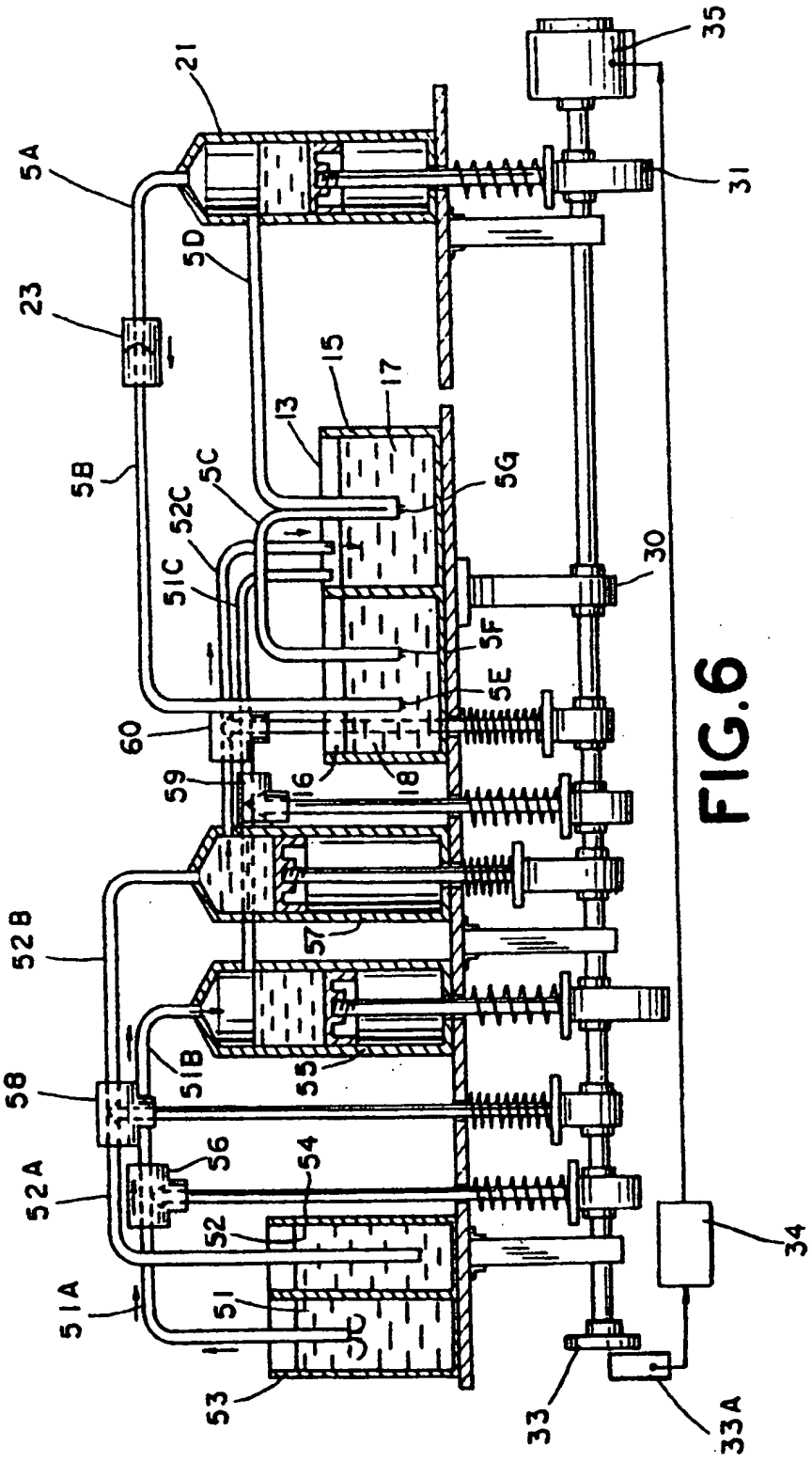
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FIG.6

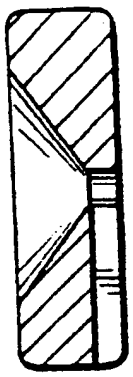

FIG.7A

FIG.7B